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ON THE OCCURRENCE, SITES AND MODES OF ORIGIN AND DESTRUCTION, OF PRINCIPLES AFFECTING THE COMPENSATORY VASCULAR MECHANISMS IN EXPERIMENTAL SHOCK[1, 2]

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THE possibility was recognized by Cannon, Bayliss *et al.*[4] during World War I that positive deleterious principles might arise during hemorrhagic and traumatic shock, in consequence of the reduction in blood volume or tissue damage, and contribute to the fatal outcome. However, since little direct evidence has been forthcoming in support of this concept, there has been a growing tendency during recent years to emphasize the primary importance of the reduction in the effective blood volume and its direct circulatory consequences, to the exclusion of other factors.[5]

[1] The major portion of this material was presented at a conference on shock held under the auspices of The Josiah Macy, Jr. Foundation at Boston, May 14, 1945. Submitted for publication October 1, 1945.

[2] The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College. It was also aided by a grant from The Josiah Macy, Jr. Foundation to New York University. During the past summer, additional support and the facilities of the Lilly Research Laboratories, Woods Hole, Mass., were made available through Dr. G. H. A. Clowes, of the Eli Lilly Company.

[3] With the technical assistance of Mathilda Fischl and Leon Dziorney.

[4] W. B. Cannon, "Traumatic Shock," D. Appleton and Co., 1935.

[5] A. Blalock, "Principles of Surgical Care; Shock and Other Problems," C. V. Mosby Co., 1940.

Nevertheless, many phenomena observed in clinical and experimental shock appear to require a more adequate explanation, particularly those conditions leading to a state increasingly refractory to fluid replacement therapy; a condition which not only occurs in clinical shock, but which can be regularly induced in animals by certain standard experimental procedures. Nor can the fluid-loss concept explain the decreased tolerance to fluid loss and hypotension in traumatic as compared with hemorrhagic shock, or the death from tourniquet shock of animals whose limbs have been tightly taped to prevent significant fluid loss.

Attempts have been made, from time to time, to assign a definite role in shock to a variety of known agents derived from tissues, but none of these produce specific or systemic effects relating them directly to the changes observed in the conventional shock syndrome. Studies directed at the possible deleterious effects of metabolic derangements or tissue products resulting from reduced oxygen tensions in shock have revealed alterations in the chemical composition of the blood, which apparently reflect the relatively anaerobic character of metabolism during shock.[6] Thus far, however, except for the experimental data cited below, it has not been possible to causally relate any of these changes to the progressive development of irreversibility.

Recently, Chambers, Zweifach and their associates,[7,8] using the vascular reactions of the exteriorized omentum and mesentery as an index, have found that the shock syndrome in anesthetized animals subjected to prolonged hemorrhagic hypotension or to traumatic procedures consists of two stages, an initial compensatory and a subsequent decompensatory phase, referable to humoral factors with opposite actions. The initial phase was characterized by an increase in the frequency and amplitude of the intermittent constrictor activity (vasomotion) of the metarterioles and precapillary sphincters and in their heightened reactivity to epinephrine. The maintenance of this type of hyper-reactivity was favorable to the compensatory vascular adjustments to reduced blood volume, since, by confining the capillary blood flow to main thoroughfares, it served to insure an adequate venous return from the tissues. With the prolongation of the profound hypotensive state, hyper-reactivity was gradually superseded by a state of hypo-reactivity, characterized by a progressive depression in the reactivity of the terminal arterioles and precapillaries, antagonistic to the compensatory vasomotor adjustments which had prevailed during the initial stage of the syndrome. As a result, the peripheral blood flow was no longer confined to main vascular channels, but through loss of precapillary sphincteric control overflowed into the capillary bed; this, in turn, led to progressive venular stagnation and eventual failure of the peripheral venous return to the heart. Once this hyporeactive phase had fully developed, replacement therapy had only a transient effect; a state of irreversibility or failure to respond to transfusion having been reached. That humoral factors were responsible in large measure for both vaso-excitor and vaso-depressor effects was evident from their passive transference to anesthetized normal rats, where they produced corresponding effects on the vessels of the meso-appendix.

The development and persistence of a humoral vaso-depressor principle of this type in shock would appear to furnish a logical explanation of irreversibility. Its vascular effects are essentially decompensatory in nature. By interfering with the peripheral vaso-constriction essential for the maintenance of an adequate blood pressure and setting up conditions permitting the pooling of blood in capillaries and venules, it initiates a morbid cycle leading to a progressive decrease in the effective circulating blood volume. Once the vaso-depressor factor is dominant, transfusions could be expected to exert only a brief check on this morbid cycle and then to become lost from the effective circulation in the manner described above.

This novel and important contribution to the theory of shock provided the stimulus for the present studies. The experiments were designed to explore this concept further and, specifically, to investigate the sites of origin of these vaso-excitor and vaso-depressor principles as well as the mechanisms leading to their formation and destruction. The reasoning which guided our experimental approach may be briefly set forth. Since these principles were demonstrably circulating in the blood stream, their origin should be sought in the tissues of the shocked animal, from which they might be extracted under appropriate conditions. The sequence of their appearance in the blood should reflect the order of their production in the tissues. In considering the possible mechanism which might be responsible for their genesis, the most attractive, because most consistent, was the reduced oxygen tensions prevailing in the tissues during shock. This concept would be verified if the exposure of normal tissues to anaerobiosis *in vitro* resulted in the formation of similar principles. Finally, the ability of tissues to destroy these factors and the conditions under which destruction took place could be explored by similar *in vitro* experiments.

The utilization of the rat meso-appendix technique

[6] F. L. Engel, *Jour. Mt. Sinai Hospital*, 12: 152, 1945.
[7] B. W. Zweifach, R. E. Lee, C. Hyman and R. Chambers, *Ann. Surg.*, 120: 232, 1944.
[8] B. W. Zweifach, R. G. Abell, R. Chambers and G. H. A. Clowes, *Surg., Gyn. and Obstet.*, 80: 593, 1945.

of Zweifach and Chambers[9] for the detection of vaso-excitor or vaso-depressor activity in blood or tissue extractives provided a unique means for effecting a direct correlation between *in vivo* and *in vitro* phenomena. An evaluation of the nature and extent of such activity was made by following the changes in the responsiveness of the terminal vascular vessels to the topical application of epinephrine.

Intensity was graded by noting the concentration of epinephrine just sufficient to elicit an unmistakable constriction of the metarterioles in the meso-appendix after intravenous injection of the test samples and comparing it with that which had been required to effect a similar vaso-constriction in the control state before injection. *Duration* was measured by noting the time required for the vessels to regain their original reactivity. In keeping with the general character of this presentation, it has seemed adequate to express the effects observed as absent, slight, moderate or marked; and the abbreviations, VDM and VEM, will usually be used for vaso-depressor and vaso-excitor material respectively. The remainder of the technical procedures were those conventionally employed in the study of tissue metabolism and can most conveniently be described in connection with the experimental data.

SITES OF ORIGIN OF THE VASO-DEPRESSOR AND VASO-EXCITOR PRINCIPLES

The purpose of these experiments was to trace these humoral principles back to the tissues from which they were derived. Dogs in hemorrhagic and tourniquet shock and rabbits in tourniquet shock provided the material for these studies. Except when specifically noted, the dogs and rabbits were maintained under sodium pentobarbital anesthesia. Blood pressures were recorded from the femoral artery in order to insure fulfilment of the criteria for induction of irreversible shock. Blood samples were tested at frequent intervals for VEM and VDM, and at appropriate times during both compensatory and decompensatory phases a variety of tissues were removed for the preparation of saline washes. Thin slices of liver, heart, kidney and spleen and thin sheets of intestinal smooth muscle were prepared immediately after removal and shaken for 2–7 minutes with 5 parts by volume of iced physiological saline. Skeletal muscle was prepared for extraction by careful dissection of individual muscle fibers from the hind limbs just prior to sacrifice. Saline washes were cleared of cellular debris by centrifugation and used, as was serum, in 0.5 cc amounts for the rat meso-appendix test.

Since the major concern of these studies lay in the further exploration of the relation of the vaso-depressor principle to the condition of irreversible shock, emphasis will be given to the data bearing on this question.

The first group of experiments was designed to provide an answer to the question as to whether the production of VDM was a property common to all tissues or restricted to specific organ systems. To this end, tissues were removed for analysis from dogs and rabbits in the hypo-reactive, decompensatory stage of tourniquet and hemorrhagic shock, when VDM could be demonstrated in the blood stream. Saline washes of spleen, cardiac and smooth muscle were uniformly devoid of activity; those from kidney exhibited a profound vaso-excitor effect. Liver and skeletal muscle, however, invariably contained significant amounts of VDM, similar in its action on the vascular bed of the meso-appendix to VDM in serum from shocked animals. The concentration of VDM was always greater in liver washes made by shaking one part of tissue with five parts of saline than in serum simultaneously removed from the same animal, and similarly diluted with five parts of saline. An appreciable amount of VDM was found in skeletal muscle during hemorrhagic shock. This amount was considerably less than that found in the livers of such animals. Much larger amounts of VDM were found in the muscle in tourniquet shock. When skeletal muscle fibers were dissected out *in situ* before release of a five-hour hind-limb tourniquet, saline washes contained considerable amounts of VDM. Likewise, skeletal muscle washes obtained during the hypo-reactive stage two to four hours after release of the tourniquets contained approximately the same amounts of VDM as did the liver washes at this stage. Control studies on saline washes of tissues derived from normal animals were essentially negative.

It seemed reasonable to infer from these experiments that the VDM present in the blood during the hypo-reactive stage could be derived only from liver and skeletal muscle. In order to further relate the production of VDM to irreversibility, a second group of experiments was carried out to determine to what extent its production was confined to the hypo-reactive stage. Saline washes were made of a comparable series of tissues removed in the initial compensatory phase of shock, when only VEM could be detected in the circulation. No VDM was found in liver washes either in hemorrhagic or tourniquet shock. Skeletal muscle washes from dogs in this phase of hemorrhagic hypotension contained a small amount of VDM, which varied with the duration of the limb ischemia. Tourniqueted muscles likewise contained appreciable amounts of VDM. Kidney washes

[9] R. Chambers, B. W. Zweifach, B. H. Lowenstein and R. E. Lee, *Proc. Soc. Exp. Biol. and Med.*, 56: 127, 1944.

always elicited marked vaso-excitor responses. The remaining tissues were either neutral or contained scant quantities of VEM, probably due to blood contained in the organ. To determine whether the absence of VDM from the liver during the initial hyper-reactive stage might merely be due to the relatively short interval between the initiation of shock and the removal of the tissues, hemorrhagic shock was induced in unanesthetized animals. Such animals, if not treated with blood or plasma, persist in a hyper-reactive stage with only VEM in the blood until exitus and invariably respond favorably to transfusion. Livers removed from these hemorrhagic animals after as much as three hours of profound hypotension were likewise devoid of VDM.

The notable difference between the compensatory and decompensatory phases of shock with respect to the formation of VDM resides in the finding that no appreciable amount of VDM appears to be produced by the liver until after the onset of the hypo-reactive or irreversible stage. Two important implications of this observation may be pointed out. It suggests that the transition to the irreversible state is coincidental with and/or conditioned by the initiation of VDM production by the liver; and that the major portion of humoral VDM present during the hypo-reactive stage is derived from the liver. It is not possible at the present time to reconcile the presence of VDM in the limbs, particularly in tourniquet shock, during the hyper-reactive stage, with its absence from the circulation. It may be released in amounts too small to detect, because of the reduced blood flow in the extremities, or masked by the preponderance of humoral VEM; or, as will be shown later, it may be destroyed by the liver as rapidly as it is released into the circulation.

Before leaving this aspect of the study, brief consideration should be given to the relation of the kidney to the hyper-reactive phase of shock. Since the action exerted on the terminal vascular bed by VEM, present during this phase, is compensatory in character, its exclusive formation in the kidney would represent a major contribution by that organ to the maintenance of an effective circulation in the face of a reduced blood volume. Further evidence of the dependence on the kidney for the largest fraction of humoral VEM was provided by experiments on dogs after complete renal occlusion. They went into profound shock more rapidly than normal animals. Those in hemorrhagic shock tolerated less blood loss, and had only minimal amounts of VEM in the blood stream. VEM was entirely absent in those in tourniquet shock, and large amounts of VDM appeared with unusual rapidity. Apparently, the kidneys contribute not all, but certainly the major amount, of VEM. Other possible sources of similar excitor materials, particularly the pituitary and adrenals, are under investigation.

Mode of Origin of Vaso-depressor and Vaso-excitor Principles in Shock

Although experiments with saline extracts of tissues obtained from shocked animals served to localize the sites from which these principles were derived, they could provide only inferential evidence as to their mode of origin. The reduced oxygen transport to the extremities and abdominal viscera in shock seemed to offer the most likely explanation for their genesis; yet it was obviously impossible to exclude the participation of other, as yet unknown, factors. These considerations led to the utilization of *in vitro* methods to test the hypothesis that these agents might arise from metabolic derangements resulting from tissue anoxia, *per se*.

Accordingly, the same group of tissues taken from normal dogs and rabbits were prepared for *in vitro* studies in the manner described above and exposed to complete anaerobiosis for varying lengths of time, at 37.5° C. They were kept in either Krebs-bicarbonate medium or serum at pH 7.4, in an atmosphere of 95 per cent. N_2–5 per cent. CO_2. The usual period of exposure was 2 hours. The supernatants were then cleared of cellular debris and tested for VDM and VEM. Control experiments were carried out simultaneously in an atmosphere of 95 per cent. O_2–5 per cent. CO_2.

The *in vitro* results were in complete agreement with those with tissue extracts from shocked animals. Supernatants from spleen, cardiac and smooth muscle were entirely negative. Kidney uniformly produced VEM both in Krebs solution and in serum. Liver and skeletal muscle invariably produced VDM, similar in action on the vascular bed to VDM appearing in blood during the hypo-reactive phase of shock and in extracts of liver and skeletal muscle removed from shocked animals. The amounts formed during anaerobiosis were of the same order of magnitude as those present in washes of shock tissues. The rate of formation was much greater in liver than in skeletal muscle. With liver no VDM was detectible for about 20–30 minutes; thereafter the amounts increased quite rapidly and progressively throughout a three-hour exposure. Larger amounts appeared after incubation with serum than in Krebs-bicarbonate. Apparently complete anaerobiosis was not essential, since VDM was also formed by liver *in vitro* at oxygen tensions of 5 and 10 per cent., conditions more comparable to those prevailing in the liver during the hypo-reactive stage of shock. Cellular integrity was apparently necessary for maximal production of VDM, since only trivial amounts were formed by liver

brei under similar *in vitro* conditions. With skeletal muscle, relatively small amounts, comparable to those present in muscle extracts from animals in hemorrhagic shock, appeared after a two-hour anaerobic exposure; after five hours, the larger amounts formed corresponded to those in extracts from limbs tourniqueted for the same length of time. No VDM resulted from aerobic incubation of any of these tissues. Bacteriological studies, for which we are indebted to Dr. René Dubos,[10] excluded, in his opinion, the bacterial origin of VDM formed under these conditions.

In view of such complete agreement between the *in vivo* and *in vitro* experiments, tissue anoxia, *per se*, could supply an adequate explanation for the production of VDM and VEM in shock. The manner in which certain anesthetic agents influence the formation of these principles is under investigation. Reasons must also be found for the fact that VEM is elaborated by the kidney very early in shock, whereas the formation of significant amounts of VDM by the liver has been observed only in the hypo-reactive stage. Since anoxia leads to the formation of both principles, it may be concluded that, despite the reduced blood flow to the liver during the hyper-reactive phase, enough oxygen is transported to support an oxidative type of metabolism; whereas the reduction in oxygen supply to the kidney is sufficient to initiate anaerobic processes. A number of observations favor this conjecture. The oxygen requirements of the kidney are much higher than those of the liver; and it has been shown by *in vitro* studies that the respiration of the kidney is much more sensitive to reductions in oxygen tension than that of the liver. The blood supply ordinarily is considerably in excess of the respiratory requirements of the liver; its oxidative metabolism remains unaffected when the hepatic artery is made the sole source of supply.[11] Our own experiments indicate that the oxygen needs of the liver are met during the hyper-reactive phase, since, as will be pointed out, the respiration of liver slices obtained in that stage proceeds at a normal or even somewhat higher than normal rate. The kidney, on the other hand, has been shown by Van Slyke and Phillips[12] to suffer a profound reduction in blood flow from the very onset of the shock syndrome. Furthermore, the formation of VEM by the kidney *in vitro* proceeds very rapidly under anaerobic conditions. Additional evidence of the trigger character of the production of VEM is provided by our observation that, even after removal from normal animals, significant amounts of VEM have usually formed during the brief period of anoxia between the removal of the kidney and the preparation of the extract.

Mode of Destruction of Vaso-depressor and Vaso-excitor Principles

Once significant amounts of VDM have appeared in shock, this principle persists in the circulation until death, subject to only temporary dilution by transfusions. On the other hand, VDM injected into the normal test rat disappears from the circulation usually within 10–20 minutes, depending on its initial concentration. Does the persistence of VDM in the shocked animal result from a loss of a protective function possessed by the normal animal? Should this be the case, might not this loss constitute a critical defect and ultimately be responsible for the failure to respond to transfusions? The ineffectiveness of the temporary restoration of aerobiosis by massive transfusions in the hypo-reactive stage of shock suggests that the mechanism for the destruction of VDM has already suffered profound damage.

The *in vitro* approach appears to have provided answers to these questions. Tissues from normal animals were incubated aerobically at 37.5° C. with VDM obtained from various sources. Spleen, kidney, cardiac, smooth and skeletal muscle proved incapable of destroying VDM. On the other hand, normal liver slices invariably destroyed VDM from whatever source obtained, in the course of a 2–3 hour aerobic incubation. This held true for VDM in serum and saline washes of liver or skeletal muscle from shocked animals, as well as that formed *in vitro* by anaerobic incubation of normal liver and skeletal muscle. Destruction of VDM was thus found to be restricted to the liver.

In sharp contrast with healthy liver slices, those from animals in hypo-reactive shock, as well as normal liver slices previously exposed to anaerobiosis for two hours, destroyed only small amounts, or, usually, none at all; and occasionally even contributed additional VDM despite the aerobic conditions of the experiments. Anaerobiosis thus had two undesirable consequences for the liver; it led not only to the formation of VDM, but also to a concomitant loss of the capacity to destroy it, on subsequent restoration of aerobic conditions. An entirely different picture was presented by liver removed during the hyper-reactive stage; not only was VDM absent, but the capacity to destroy it was fully preserved.

An attempt was made to relate the respiratory metabolism of the liver to the capacity to destroy VDM. Normal liver slices which had lost this property as a result of previous anaerobic incubation were found to have sustained a profound reduction in oxygen consumption, which usually fell to 25 to 35 per cent. of the control values. Conversely, livers

[10] Personal communication, 1945.
[11] F. L. Engel, H. C. Harrison and C. N. H. Long, *Jour. Exp. Med.*, 79: 9, 1944.
[12] Personal communication, 1944.

removed during the hyper-reactive phase and which retained this function consumed oxygen at a normal rate. This apparent correlation between the over-all oxidative capacity and inactivation of VDM was, however, not borne out by similar studies with liver removed during the hypo-reactive stage. Here the total loss of capacity to destroy VDM was frequently associated with a reduction in oxygen consumption of as little as 15–20 per cent. below the average control values. Destruction of VDM would therefore appear to be a function of some specific, and probably enzymatic, system in the liver which is extremely sensitive to anoxia. Further support for this assumption is furnished by our success in preparing a cell-free extract from normal liver, by methods which will be described elsewhere, which has proved capable of destroying VDM on aerobic incubation *in vitro*.

The fate of VEM in the shocked animal was also explored by *in vitro* methods, in an attempt to provide an explanation for its gradual disappearance from the blood stream. Since its actions are such as to assist the compensatory vascular mechanisms by which the capillary bed is kept ischemic and the reduced blood volume confined within the main vascular channels, its loss puts the organism at a disadvantage in its efforts to maintain an effective circulation. One important mechanism not susceptible to *in vitro* analysis is the probable inaccessibility of kidney VEM to the blood stream as a result of the progressive and profound reduction in renal blood flow characteristic of the shock syndrome. Several other limiting factors have, however, been disclosed by the exposure of VEM to a variety of tissues *in vitro*. Liver and kidney slices inactivated VEM on aerobic incubation; kidney appeared to possess the additional property of inactivating VEM during the latter stages of prolonged anaerobiosis.

VEM production and destruction by kidney under anaerobic conditions may be described in some detail in view of their possible relation to the disappearance of vascular hyper-reactivity. When the kidney is exposed to anaerobiosis *in vitro*, the formation of VEM takes place with great rapidity, and reaches a maximum in about an hour; thereafter production gradually diminishes and ceases altogether after the second hour, even in the presence of freshly replaced serum substrate. With the further prolongation of anaerobiosis, the VEM previously formed gradually disappears. Presumptive evidence of the anaerobic destruction of VEM *in vivo* has also been obtained. Kidneys removed from animals in the hyper-reactive, as well as in the hypo-reactive, stage unprolonged by large transfusions invariably contained significant amounts of VEM. When, however, dogs were maintained in the hypo-reactive stage of hemorrhagic shock for long periods by means of repeated small transfusions, the kidney contained minimal amounts of VEM or none at all. These kidneys, on subsequent anaerobic incubation *in vitro*, no longer produced VEM. Thus, at least four factors were found to contribute to the disappearance of VEM from the circulation—aerobic destruction by the liver and kidney, limited accessibility to the circulation due to reduced renal flow, limited anaerobic production by the kidney, and eventual disappearance with prolongation of renal ischemia and anoxia.

It might be appropriate at this time to inquire into the significance of the disappearance of VEM from the circulation for the development of the hypo-reactive or irreversible stage of shock. Apparently VEM is needed for the maximal compensatory response of the peripheral vascular system. Its absence or excessive destruction in the presence of a reduced blood volume should hasten the onset of a hypo-reactive state by making it impossible for the animal to restrict the peripheral circulation sufficiently to insure an adequate venous return. As a result, a morbid cycle would be initiated through the further pooling of blood and the further reduction in circulating blood volume and blood pressure. At some time in this morbid cycle, oxygen transport to the liver should be reduced to the point where anaerobic processes would be initiated leading to the production of VDM and the development of the hypo-reactive phase.

The Relation of the Vaso-depressor Principle to the Development of Resistance to Shock

The method of inducing traumatic shock in rats by exposure to the Noble-Collip drum provides a convenient means for studying factors contributing to increased susceptibility or resistance. Under standard conditions, the mortality rate is directly related to the number of revolutions, and resistance to drum trauma can be regularly induced by repeated sub-lethal exposures. Our studies were concerned with the possibility that mechanisms associated with VDM formation and destruction might be involved in the development of increased susceptibility and resistance to this type of shock.

It was first necessary to determine whether VDM was produced in shock in rats, as well as in dogs and rabbits. This was found to be the case. Following graded exposures to the Noble-Collip drum, saline washes of livers removed immediately or 30 minutes after drumming yielded VDM in amounts proportional to the number of revolutions and expected mortality. The effects of this VDM on vascular reactivity were indistinguishable from those observed with VDM obtained from dogs and rabbits. Under *in vitro* conditions, normal rat liver also duplicated

the anaerobic production and aerobic destruction of VDM, previously observed with normal livers from dogs and rabbits.

For the study of the relation of VDM production to resistance, 3 sets of rats were used: normal rats on a Purina Chow diet; rats on a low protein (5 per cent. casein) diet for 10–12 days in order to increase their susceptibility to shock[13] and rats on Purina Chow, made resistant to 1,000 revolutions by repeated sublethal exposures to drumming.[14]

The following order of susceptibility to drum shock was obtained. Rats on a low protein diet were highly susceptible, over 80 per cent. mortality occurring with exposure to as few as 300 revolutions as compared with normal rats where a similar mortality rate was not reached until the animals were exposed to 650 revolutions. Trauma-resistant rats showed only a 10–15 per cent. mortality following drumming for 650 revolutions.

The next question investigated was whether, on anaerobic incubation, liver VDM formation might proceed at different rates in these three groups of rats, relative to their varying susceptibility to shock. The interesting result was obtained that, in the course of a 2-hour anaerobic incubation, livers from the resistant group produced less VDM than the normal controls or low-protein group.

Even more significant were the observations that not only the formation, but also the inactivation of VDM by the liver was related to resistance and susceptibility to shock. Thus, liver slices from resistant rats, anaerobically incubated for two hours, retained their capacity to destroy VDM when returned to aerobic conditions in contrast to liver slices from normal controls and low-protein rats which uniformly lost their ability to destroy VDM under similar conditions. This resistance of the inactivation system to the usual destructive effects of anaerobiosis is, so far, unique; its nature remains to be investigated. The *in vitro* findings on resistant rats were reinforced by experiments in which VDM formation and destruction by liver were determined after 1,000 revolutions in the Noble-Collip drum. Not only was much less VDM present after 1,000 revolutions than in livers of normal rats given much less drumming (600 revolutions), but the livers of resistant animals retained the capacity to destroy, on aerobic incubation, the VDM which had already been formed.

A comparison was also made of the respiratory behavior of livers from these 3 groups. In contrast with the usual reduction in oxygen consumption of shocked livers from non-resistant rats, those from resistant rats after drumming exhibited a somewhat higher than normal respiratory rate. In both this respect and in the retention of the capacity to inactivate VDM, livers of resistant rats after drumming behaved like livers removed from dogs in the hyperreactive phase of shock. Much less difference was observed in the capacity of the livers from these different groups to resist the depressant effect of a previous 2-hour anaerobic incubation on the subsequent rate of oxygen consumption. After 1 hour of anaerobiosis, the respiration of livers from resistant rats was slightly, and possibly significantly, higher than that of the normal or low-protein group; this slight superiority was lost after 2 hours of anoxia. The retention of the inactivating capacity by livers of resistant rats after anaerobic incubation despite the marked reduction in respiration offers additional evidence that the inactivation of VDM is not a function of the over-all oxidative capacity of the liver, but is related to some specific process, presumably of an enzymatic character.

A further observation relevant to the association of VDM to susceptibility to shock was derived from the study of the reactivity of the terminal vascular bed of the meso-appendix of rats given the low-protein diet. The initial reactivity remained normal through the 10th day of the diet; by the 12th day, however, initial reactivity to epinephrine was depressed and the response to injected VDM was more pronounced and prolonged than in the normal controls. Thus, even without trauma, a state of diminished vasomotion and depression of response to epinephrine had already set in, and the capacity of the liver to inactivate VDM was apparently already reduced. It was of additional interest that the livers of these animals, initially pale and yellowish, rapidly became red and hyperemic following the injection of VDM, suggesting a pooling in that organ; the kidneys were also moderately congested. Similar changes have not been observed in normal rats. This engorgement of the liver following the injection of VDM is reminiscent of the congestion in that organ during the hyporeactive stage of shock.

The concordant results of a variety of experimental approaches suggest that, at least in this type of shock, resistance and susceptibility are linked to factors which not only influence the rate of VDM formation in the liver but also augment or diminish the resistance to anoxia of the mechanisms in the liver which inactivate or destroy VDM. The exact manner in which these variations are induced by training and diet should present a rich field for investigation. The possible participation of VEM in the development of resistance and increased susceptibility to shock is being further investigated to round out the picture. Preliminary experiments with rats have indicated

[13] G. Toby and R. L. Noble, personal communication, 1945.

[14] G. Toby and R. L. Noble, *Can. Jour. Med. Res.*, 22: 79, 1944.

that a prolonged low protein régime leads to a reduction in the capacity of the kidney to produce VEM.

THE VASO-DEPRESSOR PRINCIPLE AS A "TOXIC" FACTOR IN IRREVERSIBLE SHOCK; OTHER IMPLICATIONS

We are now in a position to review briefly the evidence supporting a causal relationship between the vaso-depressor principle and irreversible shock:

(*a*) The temporal association of humoral VDM with vascular hypo-reactivity and failure to respond to transfusions has been previously established by Zweifach, Chambers and associates.

(*b*) The origin of VDM has now been traced to the liver and skeletal muscle; its genesis, to tissue anoxia. The time relations of its production in these tissues to its appearance in the circulation indicate that in hemorrhagic shock the liver is the major source of VDM; in traumatic shock, the damaged skeletal muscle mass may provide an additional amount of VDM sufficient to account for the differences between these two types of shock.

(*c*) The effects of VDM are such as to interfere with the compensatory vascular mechanisms necessary to maintain an adequate circulation in the face of a reduced blood volume. Its persistence in the blood stream would set up a morbid cycle leading to a progressive and ultimately fatal reduction in effective circulation.

(*d*) Transfusions have been shown to effect only a temporary reduction in the concentration of VDM in the blood; thereafter, the morbid cycle is re-established and leads to the pooling of the transfused blood.

(*e*) The aerobic destruction of VDM by healthy liver provides a mechanism for liberating the vascular bed from the deleterious effects of VDM.

(*f*) This function is impaired in the liver of animals which have passed into the hypo-reactive phase of shock. The same environmental condition, namely, tissue anoxia, which leads to the formation of VDM also results in progressive damage to the system which can destroy it.[15]

(*g*) In one type of shock (Noble-Collip drum), variations in susceptibility have been directly related to variations in the formation of, and in the capacity to inactivate, VDM. Resistance was associated with the retention by the liver of the capacity to destroy VDM after drumming or after anaerobic incubation.

[15] Further evidence that the liver plays an important role in the development of irreversibility to transfusion is provided by vivi-perfusion experiments of Frank, Seligman and Fine. Dogs subjected to prolonged hemorrhagic hypotension were vivi-perfused from the carotid artery of a donor through the jugular or splenic vein for a period of 2–3 hours. It was possible to prevent the development of irreversibility by vivi-perfusion of the liver, whereas controls perfused through the jugular vein died soon after transfusion. (Personal communication.)

It may be asked whether VDM constitutes the only toxic factor which can be specifically related to the development of irreversibility. A number of blood[16] and tissue extractives have, from time to time, also been suggested as specific toxic agents in shock. These include histamine, potassium, callicrein,[17] adenylic acid, adenosine triphosphate,[18] acetylcholine and bacterial toxins, particularly those formed by Clostridia[19] under anaerobic conditions prevailing in damaged muscle. Although many are capable of producing hypotension and a variety of vascular effects and several are lethal in high concentrations, all were found to differ in at least one essential respect from VDM; none lowered the reactivity of the metarterioles and precapillaries to epinephrine. Since reduced responsiveness to epinephrine is an invariable characteristic of the hypo-reactive stage in the conventional shock syndrome, it would seem justifiable to require of a suspected toxic factor that it reproduce the decompensatory vascular phenomena which are consistently present during this phase of shock. This does not preclude the possibility that some of these agents may, under special circumstances or in non-specific fashion, contribute to the lethal outcome, just as increased blood viscosity resulting from hemoconcentration, while not essential for the development of irreversibility, will intensify the decompensatory effects of VDM.

Several questions have arisen in our minds with respect to terminology. The terms "vaso-depressor" and "vaso-excitor" have been selected for these principles as descriptive of their property of either depressing or enhancing the reactivity of the terminal vascular bed to epinephrine, as well as influencing in a similar manner the vasomotion of the metarterioles and precapillary sphincters. We suspect that these effects are achieved indirectly, by the potentiation or inhibition of the fundamental reactions which govern the behavior of the smooth musculature of these blood vessels. While the term "toxic" could legitimately be applied to the end results of the action of the vaso-depressor principle in shock, it would be an inappropriate designation for the principle itself unless it could be shown to constitute a pathological product of metabolism peculiar to shock. Observations of a preliminary character have indicated that this is not the case and that the vaso-depressor material will prove to be a physiological principle, detrimental to

[16] H. N. Green and H. B. Stoner, *Jour. Physiol.*, 103: P30, 1944.

[17] W. W. Westerfeld, J. R. Weisiger, B. G. Ferris, Jr. and A. B. Hastings, *Am. Jour. Physiol.*, 142: 519, 1944.

[18] M. Bielschowsky and H. N. Green, *Nature*, 153: 524, 1944.

[19] J. C. Aub, A. M. Brues, R. Dubos, S. S. Kety, I. T. Nathanson, A. Pope and P. C. Zamecnik, *War Med.*, 5: 71, 1944.

the compensatory vascular mechanism in shock only as a consequence of the excessive concentrations reached.

These observations, as well as a consideration of the specific effects of the VEM and VDM on the terminal vascular bed, have led us to entertain the hypothesis *that the vaso-excitor and vaso-depressor principles are oppositely acting components of a homeostatic mechanism participating in the regulation of peripheral blood flow and blood pressure.* The renal vaso-excitor is very probably similar to or identical with the renin-angiotonin system, to judge from their action on the terminal vascular bed. The hypertensive effects of angiotonin have been securely established; what has hitherto been lacking is its physiological hypotensive counterpart. The vaso-depressor principle of hepatic origin fulfils, with respect to its action on the terminal vascular bed, the requirements of an antagonist to the renal vaso-excitor principle. The former depresses, the latter enhances the vasomotion and epinephrine reactivity of these blood vessels. The former increases the relative duration of the dilator phase of vasomotion in the metarterioles and precapillaries, thereby reducing peripheral resistance; the latter prolongs the constrictor phase and increases peripheral resistance. By virtue of these vascular effects, a shift in equilibrium towards the predominance of the hepatic vaso-depressor would favor the development of hypotension, while the preponderance of the renal vaso-excitor would predispose towards a hypertensive state. The competition between these two principles for the control of the terminal vascular bed is seen during the progression of the shock syndrome, particularly in the transition from the hyper- to the hypo-reactive phase.[8] During this transitional stage, both principles are present in the blood stream, but their concentrations are such as to balance one another, thus permitting the vascular bed to briefly resume a normal type of reactivity. While their concentrations during this phase of shock are undoubtedly much higher than under normal conditions, this may represent the type of equilibrium prevailing at normal blood pressure levels in the healthy organism. Should such prove to be the role of this new liver function in the economy of the organism, we would suggest the name "hypotensin" for the hepatic vaso-depressor we have described. The validity of this vascular homeostatic concept is now under investigation in a variety of experimental and clinical conditions.

THERAPEUTIC IMPLICATIONS

What are the therapeutic implications of these studies for the management of experimental shock which has become unresponsive to transfusion? At least two requirements of a successful therapeutic régime, not met by fluid replacement alone, have been revealed. The immediate goal consists in the liberation of the vascular bed from the decompensatory influence of VDM; the ultimate, in the arrest and reversal of the progressive dysfunction of the liver with respect to VDM formation and inactivation, which results from prolonged anoxia. Once these ends were attained, transfusions would be rendered capable of restoring an effective circulation and increasing peripheral resistance sufficiently to maintain an adequate blood pressure. With these requirements in mind, certain procedures have suggested themselves as a basis for further investigation.

The immediate problem of freeing the vascular bed from the deleterious influence of VDM can be approached in several ways. It might be possible to antagonize its actions by supplying VEM in amounts sufficient to insure the resumption of the compensatory type of vascular reactivity, which in turn would lead to the restoration of an adequate blood flow to the tissues, particularly to liver and kidney. The re-establishment of aerobic conditions in the liver should, to judge from *in vitro* experiments, halt any further production of VDM, thereby limiting the problem to the counteraction or inactivation of the VDM which had been previously released into the circulation. In addition to direct antagonism by VEM, the possibility should also be considered of inactivating VDM in the blood stream by appropriate agents. Mention has already been made of a cell-free liver extract which has proved capable of inactivating VDM under aerobic conditions *in vitro*.

The success of any of these procedures would ultimately depend on whether or not they eventually led to the reversal of the liver disability with respect to VDM formation and inactivation. *In vitro* studies have shown that the restoration of aerobiosis for as long as 3 hours to liver slices from shocked animals, is unsuccessful in repairing the damage to the inactivating mechanism. These experiments are supported by the results obtained by Frank, Seligman and Fine[20] with animals in irreversible shock, given infusions containing angiotonin for relatively short periods of time (2–3 hours); the beneficial effects of angiotonin on blood pressure and cardiac output did not persist much beyond the period of administration. The possibility is not excluded that spontaneous repair of the liver defect might eventually take place, were these measures sufficiently prolonged. However, in addition to the restoration and maintenance of aerobic conditions, the liver might still require support in the form of specific liver enzymes or substrates, to enable it to recover from the damage sustained. Some or all of these agents appear to be

[20] Personal communication, 1944.

present in the liver extracts mentioned above, to judge from their *in vitro* inactivation of VDM.

One further therapeutic possibility may also be profitably explored. The importance of the waning humoral concentration of VEM for the development of hypo-reactivity has already been emphasized. It was also pointed out that the capacity of the kidney to form VEM was definitely limited, not only under anaerobic conditions *in vitro,* but also in shocked animals maintained for long periods in the hypo-reactive phase. Consideration should therefore be given to measures which might enhance the endogenous formation of VEM by kidney and thus permit the spontaneous restoration of a state of equilibrium between VEM and VDM, by which the decompensatory vascular effects of the latter would be abolished.

It is evident that the investigation of these potential therapeutic procedures, as well as the vascular homeostatic concept which has been advanced, will be greatly accelerated by the elucidation of the chemical nature of VEM and VDM as well as by the isolation of the enzyme systems and substrates concerned with their production and inactivation. We wish to make clear that our present experimental results and the inferences we have drawn from them pertain only to hemorrhagic and traumatic shock in animals; and that it would be premature to extend them, at this time, to the condition of shock in man.

OBITUARY

EDWARD WILBER BERRY

February 10, 1875–September 20, 1945

THE death on September 20, 1945, of Edward Wilber Berry brought to a close one of the most unusual careers in American science, that of a man with little formal education who became a notable figure in university life and a leader in the science of geology.

Born on February 10, 1875, at Newark, N. J., he was educated in the local schools, completing his formal education with the high school in 1890. Shortly afterward he became a cotton goods salesman, remaining in this profession for seven years. He then went into newspaper work, spending the eight years from 1897 to 1905 as president, treasurer and manager of the Passaic (N. J.) *Daily News.* He had had from boyhood a bent toward rocks and fossils that developed while he was still a journalist into a keen amateur talent for paleobotany. The period from 1902 to 1905 was marked in his scientific career by a series of papers on the paleobotany of New Jersey, some descriptive, some philosophical. This work attracted the attention of Professor W. B. Clark, head of the Department of Geology at the Johns Hopkins University and State Geologist of Maryland, who in 1905 brought Berry to Baltimore to help prepare reports on the Cretaceous deposits of Maryland. In 1907 Berry was appointed assistant in paleobotany at the Johns Hopkins University, progressing from this beginning to become professor of paleontology in 1917, dean of the faculty of philosophy in 1929, and provost of the university in 1935. He had been appointed geologist with the U. S. Geological Survey in 1910 and assistant state geologist of Maryland in 1917. He retained all these connections until his retirement in 1942.

He married Mary Willard in 1898 and found in her a faithful consort, whose sudden death in 1939 was a severe blow to him. Two sons survive, Professor E. Willard Berry, of Duke University, and Dr. Charles T. Berry, of Stonington, Connecticut.

Berry's scientific work earned him honors from many organizations. He was president of the Paleontological Society in 1924. He was president of the Geological Society of America at the time of his death. He was a fellow of the American Academy of Arts and Sciences, American Association for the Advancement of Science, American Society of Naturalists. He was a member of the National Academy of Sciences, the American Philosophical Society, the Washington Academy of Sciences, the Torrey Botanical Club, Société géologique de France, Academia nacional de ciencias en Córdoba (Argentina), Sociedad geológica del Perú. He was awarded the Walker Prize of the Boston Society of Natural History in 1901, the Mary Clark Thompson Medal of the National Academy in 1944. Lehigh University gave him an honorary doctorate of science in 1930.

The scope of Berry's work was wide, and his volume of production stupendous—the total product of his activities is some 500 articles, ranging from short notes to extensive treatises. He began with the paleobotany of the Mesozoic deposits of the northern Atlantic Coastal Plain, expanding through his connections with the Federal Survey and some of the State Surveys to include in his descriptive studies ultimately the floras of the Mesozoic and Cenozoic deposits of the whole area of the Atlantic and Gulf Coastal Plains. Out of these descriptive studies came many discussions of phylogeny and other philosophical aspects of paleobotany. Occasionally he dealt with Paleozoic floras also. Collections of fossil plants from various parts of Latin America came early into his hands, turning his attention to those regions and leading him eventually to make several trips to South America, an extensive tour in the Andean region in

1919, and a summer in Venezuela in 1934. His studies touched eventually almost every country south of the United States, a first paper on the Canal Zone reaching publication in 1914 and the last several papers on fossil floras of South America, in 1945. As a teacher of general paleontology he was well informed outside his special field, this interest leading to several papers on fossil vertebrates, and several on the invertebrates, and ultimately to a textbook on general paleontology, published in 1929. Even in his busiest period as teacher and administrator, he found time to make at least a few contributions every year. It is a record few can achieve in any field.

As an individual Berry was a man of penetrating intelligence and personal charm, a fearless personality and an independent thinker, always a nonconformist and somewhat of a rebel. He had few pretensions to greatness—he preferred to be addressed as "Mister" and was known to rebuke those who persisted in calling him by other titles. His criticisms of those with whom he differed were often vigorous to the point of harshness, sometimes even unfair. Yet beneath this all he was really a kindly and amiable man.

As a university administrator his strong personality at times led him into disagreements with the faculty, with the student body, and with the sports-writers. The "degree-less dean," as the newspaper reporters were fond of calling him, was, however, a successful administrator.

As a scientist Berry was a resourceful and indefatigable worker, as the volume of his publications testifies. Perhaps owing to his newspaper experience, he wrote his manuscripts rapidly and apparently did little revising, a trait that at times betrayed him into unexpected obscurities of expression and faults of syntax. However, his writing was in general forceful and always interesting.

As a teacher he was vigorous, inspiring and generally provocative. He had strong convictions and maintained them stoutly, sometimes with caustic sarcasm. He taught his students to seek a solid foundation for their work, to refuse to accept too complacently the weight of authority, and to work out for themselves the answers to problems. One curious trait was his persistent discouragement of his students' taking up paleobotany as a professional field—he had only one student who, much against Berry's wish, became a paleobotanist. His thirty-odd years of teaching, however, have left a large body of men who look back with both respect and affection on their association with him.

There can be little doubt that Edward Wilber Berry was one of the outstanding scientists of his day. With his passing, geology, and particularly paleobotany, has lost a stalwart figure. Those who knew him have lost a very good friend.

JOHN B. REESIDE, JR.

DEATHS AND MEMORIALS

DR. MAURICE J. BABB, professor emeritus of mathematics of the University of Pennsylvania, died on October 24 at the age of seventy-five years.

PROFESSOR RODNEY B. HARVEY, for twenty-five years professor of plant physiology at the University of Minnesota, died on November 4 at the age of fifty-five years.

DR. EUGENE COOK BINGHAM, research professor of chemistry at Lafayette College, died on November 6 at the age of fifty-six years.

DR. MARGARET BARCLAY WILSON, professor emeritus of the department of physiology and hygiene of Hunter College, New York City, died on October 8 at the age of eighty-two years.

AN Associated Press dispatch reports the death at Lwow, Poland, at the age of fifty-three years, of Professor Stefan Banach, the mathematician.

A PROGRAM honoring the memory of Wilhelm Conrad Roentgen, on the fiftieth anniversary of his discovery of x-rays, was held on the evening of November 8 at the New York University College of Medicine.

SCIENTIFIC EVENTS

COMMITTEE ON THE GROWTH OF THE NATIONAL RESEARCH COUNCIL

THE appointment of a "Committee on Growth," with membership designed to be broadly representative of the fields concerned in cancer research, both basic and clinical, has already been announced by the National Research Council of the National Academy of Sciences. The committee was created, within the Division of Medical Sciences of the council, as a result of action by the American Cancer Society designating the academy as its scientific adviser for research.

The committee wishes to call the attention of interested investigators to the general outline of endeavor which it proposes to foster and the general principles by which it will be guided. The committee accepts the interpretation of its field of interest as including reliance on, contact with and support of research in the basic sciences bearing broadly on the whole phenomenon of growth.

The committee has adopted the following major principles by which, in so far as possible, it will be guided in its sponsorship of research and training programs:

(a) Desirability of long-term grants to projects of major importance.
(b) Grants, where possible, of such magnitude as to permit individual investigators to appoint associates for long-term training periods.
(c) Granting of fellowships to institutions for training of workers to acquire new techniques and wider experience.
(d) Maintenance of continuing individual contact with workers in field.
(e) Provision, on a participating basis, for continuing economic security for professional workers.
(f) Liberal attitude toward the investigator's work, his publication and reports.

To assist it in the fulfilment of its advisory functions the committee, on its part, will make free use of either *ad hoc* or standing sub-committees in specific fields of interest. Furthermore, it proposes to arrange conferences of competent groups for discussion of problems, for interchange of reports, etc.; to make surveys to analyze problems or to determine progress in areas of special interest pertaining to cancer; to evaluate, through study by sub-committees and by the main committee, basic and clinical research undertakings, and submit recommendations for support to the American Cancer Society; to initiate and plan broad or specific programs of basic and clinical research, through activities of the sub-committees and main committee, and to secure the cooperative efforts of investigators in the general undertakings.

The committee has established a central office in the Washington headquarters of the council, where information on all phases of cancer research will be assembled and from which reports may be distributed to interested investigators.

Many members of the committee have participated intensively in the broad programs of research conducted under the pressure of war. It is both the hope and the sanguine expectation of the committee that the fruitful pattern of cooperative investigations so successfully established during the war years can now be carried on, modified and tempered to existing needs, into the continuing war against disease.

Membership of the committee, as now constituted, includes the following: Dr. C. P. Rhoads, *Chairman;* Dr. Florence R. Sabin, *Secretary;* Dr. A. R. Dochez, Dr. A. Baird Hastings, Dr. Charles B. Huggins, Dr. Donald F. Jones, Dr. C. C. Little, Dr. Carl R. Moore, Dr. John J. Morton, Dr. James B. Murphy, Dr. Eugene P. Pendergrass, Dr. Howard C. Taylor, Jr., Dr. M. A. Tuve and Dr. M. C. Winternitz.

PHILIP S. OWEN, M.D.
For the Committee on Growth,
Division of Medical Sciences,
National Research Council,
Washington 25, D. C.

APPEAL FOR THE DEFERMENT OF COLLEGE SCIENCE STUDENTS

AN appeal to President Harry S. Truman to reinstate a system of deferments for college science students on a national quota basis similar to a program abandoned in 1944 has been made by the presidents of eight colleges and universities.

The policy of a national quota was established by Selective Service in Bulletin 33-6 amended in January, 1944, and effective February 2, 1944. It established an overall quota for the nation of 10,000 students to be deferred "to meet civilian needs in war production and in support of the war effort." A National Roster was established which distributed the 10,000 deferments in engineering (6,775), physics (850), chemistry (2,250), and geology and geophysics (125). The order establishing the National Roster was rescinded less than two months after it had been established, in Selective Service Local Board Memorandum 115 issued in revised form on April 4, 1944.

The letter to President Truman reads as follows:

My dear Mr. President:

This letter is an appeal to you to reinstate the system of selective deferments for college students on a quota basis which was abandoned at the height of the war emergency. We believe this has now become a matter of imperative public policy in view of the serious and increasing shortages in the ranks of those who are in training for work in the interest of public safety and welfare.

Alone of all the allied nations the United States adopted the policy of drafting from the universities all able-bodied men regardless of the occupation for which they were training. In medicine pre-professional training was discontinued in June, 1944, and unless provision is made immediately for the deferment of pre-medical students, medical school entering students in 1946 will be approximately one-half or less of normal. Pre-dental students are in an even more serious situation and, as a matter of fact, the present freshman classes in dentistry this fall are less than one-third of normal. In osteopathy and in pharmacy the facts are similar. In engineering, the total enrollment for the country in 1944–1945 was only one-fifth of normal, and in classes above the freshman year only one-tenth of normal. In spite of the critical demand of continued and intensive research in physics and chemistry the number of doctor's degrees awarded in physics in 1945 was only 20% of those given in June, 1942, and in chemistry the situation is similar. In other fields such as agriculture, biology, geology and psychology, the numbers are smaller, but the facts are equally critical.

What we face is nothing short of an alarming dearth of talent in training in those fields in which the American people are most dependent for their public health, their industrial advancements and their scientific research. It must be remembered that it is now almost a whole college generation since the flow of young scientific and professional personnel began to be impeded. Each semester that the situation is allowed to continue the dislocations

become worse and the more damage will be done to our enduring peace time programs in these essential fields.

It is not a sufficient answer to say that it will be possible to correct the shortages in these areas through the enrollment of discharged veterans. Many of those who are eligible for such courses have lost too much time to complete the long years of preparation which are necessary. With very many of these men their interest is obviously on shortening as much as possible the time between their return and the time of going to work in productive jobs.

But even that proportion that come back to college are not yet returning in sufficient numbers to make possible the rapid expansion of students in training in these areas which is essential if the United States is not to compete at a material disadvantage with the other allied nations. Such effects, it must be remembered, are cumulative, and only appear in their full effect after several years have passed. Unless immediate action is taken, we run the risk of jeopardizing our own peace time future.

The numbers thus to be reserved can be stabilized by the establishment of a national quota, with allocation to various institutions based on proportion of their normal peace time students in training in the areas in question.

We believe that we should take no further chances as a nation with the training of men for these critical fields. We are not pleading the interests of the colleges; we are concerned about what we hold to be a matter of fundamental national policy.

The policy, recently adopted by Selective Service, through which young men will not be inducted during the quarter or semester in which they become eighteen, does not meet this need. It only postpones the necessity for immediate action. If these men are inducted at the end of the term, another whole year will be lost in the training of men for these essential fields. Steps must now be taken to determine quotas and to select those who should be deferred to continue their training.

Respectfully yours,

O. C. CARMICHAEL,
Chancellor, Vanderbilt University
HARRY WOODBURN CHASE,
Chancellor, New York University
CARTER DAVIDSON,
President, Knox College
EDMUND E. DAY,
President, Cornell University
CHARLES SEYMOUR,
President, Yale University
ROBERT G. SPROUL,
President, University of California
REV. EDWARD V. STANFORD, O.S.A.,
Rector, Augustinian College,
Washington, D. C.
RAYMOND WALTERS,
President, University of Cincinnati

HONORABLE HARRY S. TRUMAN
PRESIDENT OF THE UNITED STATES
THE WHITE HOUSE
WASHINGTON, D. C.

THE PLIOCENE OGALLALA FORMATION AND ASSOCIATED QUATERNARY DEPOSITS

THE geology and geomorphology of the Pliocene Ogallala Formation and associated Quaternary deposits were studied during the week of August 15 in the field by Dr. Maxim K. Elias, paleontologist of the Nebraska Geological Survey; Dr. John C. Frye, assistant state geologist of Kansas; C. Richard Murray and Utley N. Benge, geologists, Division of Ground Water, U. S. Geological Survey; Edward H. Templin, assistant soils inspector, U. S. Bureau of Plant Industry, and Dr. W. Armstrong Price, geologist, Corpus Christi, Texas, leader.

A side trip to Gatuña Canyon and Carlsbad, New Mexico, was led by Ronald K. De Ford, chief geologist, accompanied by Dr. W. A. Waldschmidt, geologist, Argo Oil Corporation, Midland, Texas. Specialists consulted in the field, but unable to take the trip, were Glen L. Evans and Richmond L. Bronaugh, geologists; Grayson E. Meade, vertebrate paleontologist, Bureau of Economic Geology, University of Texas, and Adolph Witte, anthropologist, Texas Memorial Museum. Others who contributed information were Dr. Kirk Bryan, geologist, Harvard University; Dr. Raymond Sidwell, geologist, and Dr. Harold M. Hefley, ecologist, Texas Technological College, Lubbock.

Definite results which can already be announced include the identification of the pisolitic lithology and occasionally fully preserved bioherms of the "algal" limestone of the High Plains Ogallala to the North in the "caliche cap-rock" of the Llano Estacado; collection of seeds diagnostic of members of the Ogallala of Kansas and Nebraska in the Ogallala of Texas, and a better understanding of the origin of "caliche" caprocks of the semi-arid regions than had been previously attained by the group.

W. ARMSTRONG PRICE

CORPUS CHRISTI, TEXAS

NEWS FROM ABROAD

DR. C. A. BROWNE, collaborator of the Bureau of Agricultural and Industrial Chemistry of the Agricultural Research Administration, sends to SCIENCE the following paragraphs taken from a letter received from Dr. H. C. Prinsen Geerligs, of Amsterdam, well-known Netherlands authority on the agriculture, technology and economics of sugar manufacture in Java, which may be of interest in connection with the accounts in SCIENCE of the atrocities suffered by European scientists during the German occupation.

We had a most terrible time in the years between May 10th, 1940, and May 5th, 1945. Our country was overrun, inundated, pillaged and ruined. We were robbed of everything; furniture, radio apparatus, etc., were stolen.

My oldest granddaughter was executed by gunfire in a German concentration camp and my oldest son carried off in captivity. His house was bombed and wrecked, but there were no casualties. As a result of all this misery my wife lost her mind; she is helpless as a child, no longer recognizes me and speaks of me as if I were her uncle or father. Our country home in Bergen was occupied by the Germans, who left it entirely empty, despoiling it of all furniture, pictures, clocks, beds, etc. Our country having been totally ruined we are in great need of woolen underwear, socks, pajamas, shirts, ladies shoes and stockings, etc.

We had to live for about a year on a diet of tulip bulbs and sugar beets. At the age of eighty-one I feel the depressing effect of these hardships and because of exhaustion am unable to do any more work.

The experiences of other men of science in the Netherlands seem to have been similar to those suffered by Dr. Geerligs. The need of warm clothing to withstand the severities of winter is especially urgent, and responses to relieve this situation among our European scientific friends should be generous.

Captain Norman C. Laffer, SnC, Mycology Section, writes to SCIENCE: Shortly after the cessation of hostilities in Europe, I addressed a letter to Dr. J. Lodder, formerly of Centraalbureau voor Schimmelcultures, and on October 31 I received the following reply:

It is already long ago since I received your letter, but immediately after our liberation I could not bring myself to write a letter. We had to find ourselves back again. Moreover it was at that time not possible to send any printed matter to America. But now I will try to retrieve my shortcomings.

In 1942 Miss Diddens' and my work in the Centraalbureau voor Schimmelcultures on the anascosporogenous yeasts was published ("Die Anaskosporogenen Hefen," 2te Halfte). I greatly regret to announce to you that my friend and collaborator, Dr. Diddens, died by accident in December, 1944. I myself am no longer working at the Centraalbureau, but I am appointed at the Netherlands yeast and spirit factory at Delft.

Mycopathologia did appear from 1938–1943 in 3 volumes. The last two years we did not see it. I greatly doubt if you would be able to get these three volumes now.

As we have been devoid of any literature during the last years, I should greatly appreciate it if you could send me some copies of articles which deal with work in relation with yeasts, published in America during the last years.

Attention is invited to the last paragraph, and I am certain that Dr. Lodder and her associates would appreciate receiving reprints at her new address, Nieuwe Plantage 34, Delft, Nederland.

Information of Dutch biologists, received from one of them, reads:

Hermann Jordan, the physiologist, died from a stroke while hiding out. The geneticists, Honing, Sirks, Tammes are all right. My informant writes: "Sirks belonged to the few professors in Groningen who played a good role in the resistance against the Germans." The same is true for the botanist Koningsberger, Utrecht, and for the zoologist Van Klaauw, who were in a concentration camp for hostages, and also for the well-known biologists in different fields, Woerdeman, Barge, Buytendijk, Bierens de Haan and Boeke, all of whom are well. Less good is the news of some others: The geneticist Stomps and the parasitologist Schuurmans Stekhoven were collaborators and are now confined. Ch. S. Hirsch, a native German, joined the Nazis and disappeared into Germany.

E. W. Brandes, head pathologist in charge of soils and agricultural engineering of the Bureau of Plant Industry, writes that he has just received a letter dated September 30, 1945, from Dr. O. Posthumus and apparently mailed *via* U. S. Navy on October 10.

Dr. Posthumus is head of the department of plant breeding of the Netherlands Indies Experiment Station, Buitenzorg, Java, and gives his address as Beatriceweg No. 30, Buitenzorg. He records the deaths of Dr. G. Booberg, director of the Agricultural Department, Sugar Experiment Station, Pasoeroean, Java (Proefstation Oost Java); Dr. (Miss) P. C. Bolle, chief of the Section of Phytopathology; Dr. G. J. de Groot, chief of the Section of Cane Breeding and Selection; and Dr. Ferman, Group-adviser (Extension Service), Cheribon Sub-Station of the Sugar Experiment Station. A part of his letter reads as follows:

After the events of the last 3½ years, we are very glad to hear something of the other parts of the world which were quite closed for us. The Japanese have isolated us so well that we even did not know how things were in the other towns of Java. Personally I came through well, but from the Pasoeroean Sugar Experiment Station Miss Dr. Bolle, Dr. Booberg, Dr. de Groot—my successor—and Dr. Ferman (groepsadviseur Cheribon) died, but my information is probably still incomplete. Most sugar factories were demolished, about 25 of the 85 were left. The production seems to have been about 350,000 tons, the home consumption, but no exact data are available at present yet.

The General Agricultural Experiment Station has also many losses. We had 78 prisoners of war and 29 civil internees. 12 and 5 died, respectively, but information is not yet complete. Treatment was very bad.

A month later Dr. Posthumus wrote to Dr. Verdoorn from the Beatrix Camp, Buitenzorg, that about 110 members of his staff were interned by the Japanese. At least 25 per cent. of the internees, including such internationally known men as Dr. P. van

der Goot, Dr. W. K. Huitema, P. N. Hackenberg, Dr. P. M. Both, H. J. te Riele and A. P. Petrie have died, some of them by execution.

The death is also reported of the following biologists in the Netherlands Indies: Dr. P. J. Eyma, taxonomist at the Herbarium of the Buitenzorg Botanic Gardens; Dr. R. C. Bakhuizen van den Brink, formerly of the Buitenzorg Herbarium; Dr. J. Gandrup, the well-known Danish botanist, formerly director of the Malang Experiment Station; Dr. J. D. ter Pelkwijk, Fisheries Research Institute, Batavia; and Dr. H. J. Vos, Laboratory for Marine Biology, Batavia.

Word has also been received that Dr. T. H. van den Honert, director of the Buitenzorg Botanic Gardens, is in a camp in Siam, in relatively good health.

In a recent letter to Dwight J. Ingle, of the Research Laboratories of the Upjohn Company, Professor T. Reichstein, Pharmazeutische Anstalt der Universität, Basel, Switzerland, stated that they have been almost completely without literature from the non-European countries for three and one-half years and that he would like to receive reprints of papers relating to sterol chemistry and to the chemistry and physiology of the hormones.

Professor G. F. Papenfuss, of the department of botany of the University of California at Berkeley, informs us that, in a letter dated October 5, Dr. Erling Christophersen, conservator of the Botanical Museum of the University of Oslo, writes that he is safe and sound, in spite of a temporary internment in Norway by the Germans. He is still working with the material brought home by the Norwegian Scientific Expedition to Tristan da Cunha in 1937–1938, of which he was leader. In some fields a good deal of the material has been published. The report of the marine algae by Baardseth appeared in 1941.

The following communication has been received from Dr. Walter C. Tobie, of the American Cyanamid Company, Stamford, Conn.:

Those engaged in the field of microbiology will be interested to learn that Professor Ph. Lasseur, of the Laboratoire de Microbiologie, of the Faculté de Pharmacie of the Université de Nancy, is still conducting his researches on the differentiation of dissociated types of bacteria and on other aspects of bacteriology. Throughout the war years, he continued to carry on his work, despite the loss of some of his cultures during the mobilization of 1939. The two journals issued by his laboratory, the *Travaux du Laboratoire de Microbiologie de la Faculté de Pharmacie de Nancy* and the *Bulletin de l'Association des Diplômés de Microbiologie de la Faculté de Pharmacie de Nancy*, were able to continue publication during hostilities. It is expected that fascicule 14 of the *Travaux* will be issued shortly.

Dr. Lasseur has written also to Dr. K. Starr Chester, of the Oklahoma Agricultural and Mechanical College at Stillwater, that "despite innumerable difficulties, moral and material, we have continued to work during these six years." Dr. Chester states that a shipment of reprints from Professor Lasseur's laboratory gives ample indication of the diligence and productivity of his group throughout the war. He also has been deprived of American publications, and requests recent reprints in the field of microbiology. Dr. Chester quotes the following paragraph from a letter written by Dr. G. O. Ocfemia, professor of plant pathology at the University of the Philippines, requesting all available reprints:

The college reopened on July 26, 1945, without any equipment and library facilities. My own collection of books and reprints on virus diseases of plants was reduced to ashes when my house was burned on March 14, 1945. We have no library facilities because the Bureau of Science Library in Manila, which was considered as the best in the Far East, was also burned.

In a letter to Dr. Carl L. Hubbs, of the Scripps Institution of Oceanography of the University of California, Dr. Canuto Manuel writes that he has rejoined the Philippine Bureau of Science. The building of the bureau, like most of the government district of Manila, lies in ruins. The library and the museum are destroyed. Publications and specimens are urgently needed, but sendings should be delayed temporarily to await facilities for proper storage. Dr. Manuel's personal belongings and library, including a list of Philippine birds that was ready for the press, are all lost. He reports that Dr. Deogracias Villadolid, who served as director of the Bureau of Fisheries during the war, has also returned to his position in the Division of Fisheries.

To Dr. E. Raymond Hall and Dr. Hobart M. Smith, of the Museum of Natural History of the University of Kansas, Dr. Edward H. Taylor writes from Selangor under date of October 5, that

Dr. Chasen of the Singapore Museum is believed dead. The boat he escaped on was sunk in the Straits. His wife and child were on another boat, which was likewise sunk. The Singapore Museum was wholly uninjured. The Museum at Taiping was looted rather thoroughly—by whom it is not known. That at Kuala Lumpur was destroyed during the bombing by the Americans. It was so close to the railway yards that practically everything had been moved to places of safety. Duplicate material and types were sent to Tring in England. The library was largely saved and a few of the exhibits. The Japanese ordered everything returned that was still here, so, unknown to the outside world, this was done. The Director of these two Museums, Mr. Pendleberry, barely survived Prisoner of War camp at Singapore and has gone to England to recuperate.

SCIENTIFIC NOTES AND NEWS

MAJOR GENERAL NORMAN T. KIRK, Surgeon General of the Army, has been awarded the Distinguished Service Medal by General Brehon Somervell, Commanding General of the Army Service Forces, in recognition of his "outstanding leadership . . . in directing the largest Medical Department in the history of the United States Army."

DR. ALBERT F. BLAKESLEE, visiting professor of botany at Smith College, has been elected a foreign member of the Royal Swedish Academy of Sciences.

DR. GARRETT BIRKHOFF, associate professor of mathematics at Harvard University, has been elected honorary associate of the Sociedad Matemática Mexicana.

AT the recent annual meeting in Cleveland of the American Society for Metals, Dr. Charles H. Herty, Jr., of Bethlehem, Pa., was elected president.

PROFESSOR PAUL H. BUCK, dean of the Faculty of Arts and Sciences, has been appointed to the newly established position of provost of Harvard University. He also will serve, *ex-officio,* as dean of the Faculty of Arts and Sciences.

DR. LEON O. JACOBSON, assistant professor of medicine at the University of Chicago, who for the past three years has been associate director of the division of biology and medicine of the metallurgical project at the university, has been appointed associate dean of the division of biological sciences.

DR. NORMAN D. NEWELL, of the department of geology of the University of Wisconsin, more recently connected with the Department of State in Peru, has been appointed to the joint position of curator of historical geology and fossil invertebrates at the American Museum of Natural History and professor of invertebrate paleontology in the department of geology of Columbia University. He will direct instruction in invertebrate paleontology at Columbia University and will have charge of the Invertebrate Fossil Collections at the museum. Students at the university will have the privilege of carrying on research making use of the facilities of the museum.

DR. ISAAC STARR, Milton Bixler Hartzell research professor of therapeutics, has been elected dean of the School of Medicine of the University of Pennsylvania. Dr. William Pepper, dean of the school for thirty-three years, will become dean emeritus.

PROFESSOR WILLIAM PHELPS KIMBALL, assistant dean and professor of civil engineering of the Thayer School of Engineering of Dartmouth College, has been appointed dean of the school.

DR. J. ROBERT OPPENHEIMER, retiring director of the atomic bomb laboratories at Los Alamos, New Mexico, has become professor of theoretical physics at the California Institute of Technology. Dr. Norman E. Bradbury, professor of physics on leave from Stanford University, has been appointed to succeed him at Los Alamos.

DR. WILLIAM F. O'CONNOR has been appointed to the newly established post of professor of safety engineering at the College of Engineering of New York University. It is planned to cooperate with the Georgia School of Technology, with the Illinois Institute of Technology, with New York University and with the University of California in a national plan to introduce safety engineering at the college level.

DRS. E. M. PURCELL, J. S. Schwinger and R. R. Wilson have been appointed associate professors in the department of physics at Harvard University.

DR. COURTNEY WERNER, of Washington University, St. Louis, has been promoted from an assistant professorship to an associate professorship of geology.

DR. HOWARD E. SHEFFER has been appointed assistant professor of chemistry at Union College, Schenectady, N. Y.

DR. EUGENE C. COYNER, formerly instructor of chemistry at the University of Minnesota, now with the Experimental Station of E. I. du Pont de Nemours and Company, Wilmington, Del., has been appointed, from January 1, assistant professor of organic chemistry at the University of Tennessee.

THE following promotions of members of the department of chemistry have been made at the University of Pittsburgh: W. E. Baldwin to an associate professorship; B. F. Daubert and Klaus Hofmann to associate research professorships. R. E. McClure has become associate professor, Hurd W. Safford assistant professor and W. E. Wallace assistant research professor. Captain Douglas G. Nicholson, C.W.S., formerly associate in chemistry at the University of Illinois, has been appointed associate professor of inorganic chemistry.

DR. PHILIP R. WHITE, after thirteen years of association with the Rockefeller Institute for Medical Research at Princeton, N. J., has resigned to accept an appointment at the Institute for Cancer Research at the Lankenau Hospital Research Institute in Philadelphia. He will organize and direct a division of general physiology and tissue culture dealing with problems in tumor growth. He will take up his new work on December 1.

THE John and Mary R. Markle Foundation has granted the sum of $7,000 to continue the support for two years of the study of filariasis under the direction of Dr. J. Allen Scott, associate professor of preventive medicine at the Medical Branch at Galveston of the University of Texas. The Sugar Foundation, Inc., of New York City, has made a grant of $1,000 for the support of research on the influence of carbohydrates on experimental liver cancer under the direction of W. A. Selle, professor of physiology.

PROFESSOR M. S. COOVER, head of the department of electrical engineering at Iowa State College, has been appointed for a term of three years representative of the Council for Professional Development of the American Institute of Electrical Engineers.

THE Board of Governors of the Arctic Institute of North America has appointed Dr. A. Lincoln Washburn director of the institute. Permanent headquarters have been opened in Montreal.

DR. VOLNEY C. WILSON, instructor in physics at the University of Chicago; Dr. John P. Howe, assistant professor in the department of chemistry of Brown University, and Dr. John F. Eckel, associate professor of metallurgy at Purdue University, have joined the staff of the research laboratory of the General Electric Company at Schenectady.

SIR JOHN BOYD ORR, Aberdeen, until his election to Parliament this year director of the Rowett Research Institute and of the Imperial Bureau of Animal Nutrition, has been elected unanimously for a two-year term director general of the United Nations Food and Agriculture Organization.

DR. P. JAMES RICH, until recently on the advisory staff of the field director of Ammunition Plants, Army Service Forces, has been appointed director of research for Blanke-Baer Extract and Preserving Company of St. Louis.

UNDER an agreement between the Fish and Wildlife Service and the University of Chicago, W. L. McAtee is in residence at the university, where he will complete a dictionary of vernacular names of North American birds to be published by the University of Chicago Press.

DR. J. OSBORN FULLER, who was granted leave from West Virginia University to work for the United States Geological Survey on an oil project in southwestern Virginia, has returned to his teaching position in the department of geology.

LIEUTENANT COMMANDER HAROLD T. COOK, USNR, returned from overseas duty on October 21 and was released from active duty on November 1. He will resume his position as head of the Department of Plant Pathology of the Virginia Truck Experimental Station, at Norfolk, on December 1. He served as officer-in-charge of the fruit and vegetable section of the Food Inspection Division, U. S. Joint Purchasing Board, in New Zealand from December, 1942, to February, 1945, and was then transferred to the Island of Tinian, where he commanded the naval unit that operated farms for the production of fresh vegetables for the military forces in the forward areas.

PROFESSOR H. MUNRO FOX, F.R.S., Professor I. M. Heilbron, F.R.S., and C. C. Paterson, F.R.S., have been appointed members of the British Advisory Council to the Committee of the Privy Council for Scientific and Industrial Research. Professor A. V. Hill, Sir Felix Pole and Sir Robert Robinson retired from the council on completion of their terms of office on September 30.

PROFESSOR I. M. HEILBRON, F.R.S., and Dr. L. H. Lampitt, the chairman and secretary of the British National Committee for Chemistry, on October 16 left on a visit to Paris to re-establish contact with French men of science. The purpose of their visit was to discuss informally the revival of international collaboration in science. Professor G. I. Finch, F.R.S., carried greetings from the Royal Society on behalf of the men of science of Great Britain to their colleagues in Belgium and Holland. It was hoped to renew and re-establish scientific contacts and to see what help could be given by British science towards the rehabilitation of science and scientific education in these two countries. In Belgium Professor Finch was the guest of the Académie Royale des Sciences, des Lettres et des Beaux-Arts in Brussels, and in Holland of the Koninklijke Akademie van Wetenschappen.

PROFESSOR C. R. LONGWELL, chairman of the department of geology of Yale University, is on a lecturing tour under the auspices of the Distinguished Lecture series of the American Association of Petroleum Geologists. Seventeen lectures will be given before groups in several states and in Alberta. The subject of the lecture is "Geology of the Basin Ranges —Revelations and Problems."

THIS year's series of the Laity Lectures of the New York Academy of Medicine, which were inaugurated on the evening of Thursday, November 8, at 8:30 P.M., is devoted to the subject "Medicine To-day." The first lecture in the series was delivered by Dr. John F. Fulton, chairman of the Advisory Board of the Historical Library of the Medical School of Yale University. Preceding Dr. Fulton's address, there was a brief presentation by Dr. Malcolm Goodridge, chairman of the Committee on Medicine and the Changing Order. The address of welcome was made by Dr. Cornelius P. Rhoads, acting president of the academy.

THE Committee on Scientific Research of the Amer-

ican Medical Association invites applications for grants of money to aid in research in problems bearing more or less directly on clinical medicine. Preference is given to requests for moderate amounts to meet specific needs. As a rule grants are not made for the purchase of equipment or apparatus of a permanent nature. For application forms and further information, the committee should be addressed at 535 North Dearborn St., Chicago 10, Ill.

THE Psycho-Acoustic Laboratory, initiated at Harvard University in 1940 as a war research unit, will continue its activities directly under the Faculty of Arts and Sciences. Funds available under a contract with the U. S. Navy, Office of Research and Inventions, will provide for basic research in experimental psychology, with special emphasis on problems of communication (speech, hearing and electronics). There will be a research and teaching staff of about twelve members, including S. S. Stevens, director, and E. B. Newman, associate director.

THE twentieth Exposition of Chemical Industries will be held from February 25 to March 2 in Grand Central Palace, New York. The exposition, on a reduced scale due to war conditions, was last convened in 1943.

THE Long Island College of Medicine, Brooklyn, N. Y., will give the fourth postgraduate course in industrial medicine from January 14 to February 1.

SPECIAL ARTICLES

STREPTOMYCES ANTIBIOTICS. III. DEGRADATION OF STREPTOMYCIN TO STREPTOBIOSAMINE DERIVATIVES

EXPERIMENTAL results indicate that streptomycin has the general constitution of a hydroxylated base (streptidine)[1] attached through a glycosidic linkage to a nitrogen-containing disaccharide-like molecule. The latter moiety of the streptomycin molecule contains a free or potential carbonyl group and a methylamino group.

The hydrolytic cleavage of streptomycin in acid solution and the isolation and characterization of the basic fragment streptidine are described in a forthcoming publication.[1] When the present formula of streptomycin, $C_{21}H_{37-39}N_7O_{12}$,[2] and the formula of streptidine, $C_8H_{18}N_6O_4$,[1] are used in an equation (I)

I. $C_{21}H_{37-39}N_7O_{12} + H_2O \longrightarrow C_8H_{18}N_6O_4 + C_{13}H_{21-23}NO_9$

involving the reaction with one molecule of water, it is seen that a product might be formed which is rich in oxygen and contains a nitrogen atom. The formula, $C_{13}H_{21-23}NO_9$, of such a product, the insolubility of streptomycin in water-immiscible organic solvents, the formation of a streptomycin trihydrochloride-calcium chloride double salt,[2] and the cleavage of streptomycin in acid solution at 25°,[1] are suggestive of the general constitution of a hydroxylated base linked glycosidically to a disaccharide-like molecule. The following experiments yielded further evidence in support of this formulation.

When streptomycin hydrochloride was treated with methanol containing hydrogen chloride, the biological activity decreased markedly. The mixture of products was separated chromatographically into streptidine hydrochloride[1] and the amorphous hydrochloride of a base, methyl streptobiosaminide dimethyl acetal hydrochloride[3]; $(\alpha)\frac{25}{D} - 143°$ (methanol).

Anal. Calcd. for $C_{13}H_{20}NO_7(OCH_3)_2 \cdot HCl$: C, 44.49; H, 7.00; N, 3.24; OCH_3, 21.6. Calcd. for $C_{13}H_{22}NO_7(OCH_3)_3 \cdot HCl$: C, 44.29; H, 7.57; N, 3.19; OCH_3, 21.5. Found: C, 44.35; H, 7.13; N, 4.00; OCH_3, 19.1; amino-nitrogen (van Slyke), none.

The cleavage of streptomycin to give a product of the formula $C_{13}H_{20-22}NO_7(OCH_3)_3 \cdot HCl$, is shown in equation II.

II. $C_{21}H_{37-39}N_7O_{12} \cdot 3\,HCl + 3\,CH_3OH \longrightarrow$
$C_8H_{18}N_6O_4 \cdot 2\,HCl + C_{13}H_{20-22}NO_7(OCH_3)_3 \cdot HCl + H_2O$

In the infrared, methyl streptobiosaminide dimethyl acetal hydrochloride in tetrachloroethane solution absorbed in the 3 μ (–OH, > NH) region; no carbonyl absorption could be detected. Since, as will be discussed below, the disaccharide-like portion of the molecule in streptomycin contains a free or potential carbonyl group, it seems likely that in the derivative of streptobiosamine described here, the original carbonyl group has been converted to a dimethyl acetal. The third methoxyl group is presumably that of a methyl glycoside.

Acetylation of methyl streptobiosaminide dimethyl acetal hydrochloride gave a crystalline acetyl derivative, m.p. 124.5–126°, $(\alpha)\frac{25}{D} - 124°$ (chloroform). Analytical and molecular weight data on material recrystallized to constant properties were in agreement with a composition $C_{13}H_{16-18}NO_7(CH_3CO)_4(OCH_3)_2$, or methyl tetra-acetylstreptobiosaminide dimethyl acetal.

[1] Peck, Graber, Walti, Peel, Hoffhine and Folkers, *Jour. Am. Chem. Soc.* (In press.)

[2] Peck, Brink, Kuehl, Flynn, Walti and Folkers, *Jour. Am. Chem. Soc.*, 67: 1866, 1945.

[3] Consideration of a convenient trivial name for this product led to the selection of streptobiosamine for the parent disaccharide-like compound. The name streptobiose would imply a neutral material rather than a base, and streptosamine would imply a nitrogen-containing hexose (similar to glucosamine).

Anal. Calcd. for $C_{13}H_{16}NO_7(CH_3CO)_4(OCH_3)_3$: C, 51.15; H, 6.62; N, 2.49; CH_3CO, 30.6; OCH_3, 16.5; mol. wt., 563. Calcd. for $C_{13}H_{18}NO_7(CH_3CO)_4(OCH_3)_3$: C, 50.97; H, 6.95; N, 2.48; CH_3CO, 30.5; OCH_3, 16.5; mol. wt., 565. Found: C, 50.88, 51.20; H, 7.09, 6.95; N. 2.55; CH_3CO, 29.7; OCH_3, 15.4; mol. wt., 530 (ebullioscopic in benzene).

A differential acetyl determination[4] showed that three of the acetyl groups were attached to oxygen and the fourth to nitrogen. The ultraviolet absorption spectrum of this compound in methanol solution showed only a low end absorption, with no maximum.

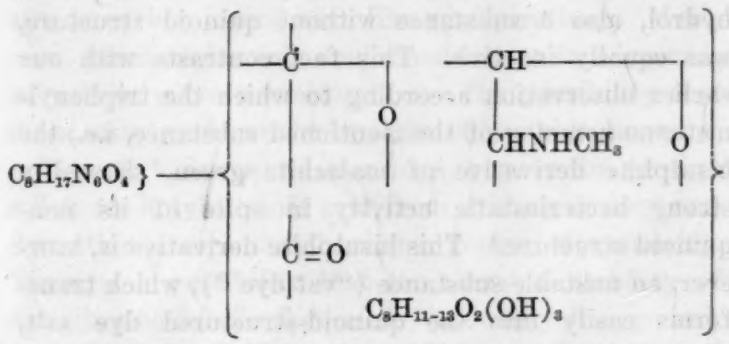
When streptomycin was treated with a variety of carbonyl group reagents, complete inactivation was observed under pH conditions which, in the absence of the reagents, caused only 50 per cent. or less inactivation. These experiments suggested that streptomycin possessed at least one carbonyl group. Streptomycin reacted with hydroxylamine to give an amorphous product having a composition in fair agreement with that of a streptomycin oxime hydrochloride. Similarly, the treatment of streptomycin with semicarbazide yielded an amorphous streptomycin semicarbazone hydrochloride. When streptomycin hydrochloride was treated with an excess of hydroxylamine hydrochloride in the presence of pyridine, an acidimetric determination of the pyridine hydrochloride formed[5] indicated that streptomycin contained a single carbonyl group. Since streptidine[1] is unreactive towards carbonyl reagents, it may be concluded that the free or potential carbonyl group of streptomycin resides in the disaccharide-like (streptobiosamine) moiety.

The failure of methyl streptobiosaminide dimethyl acetal hydrochloride to yield nitrogen in the van Slyke determination indicated that the basic nitrogen atom in streptobiosamine is not present as a primary amino group. Treatment of this compound with silver nitrite yielded an amorphous product with the properties and nitrogen content of an N-nitroso derivative. The presence of an N-acetyl group in methyl tetraacetylstreptobiosaminide dimethyl acetal afforded further evidence of the secondary character of the amino group. When methyl streptobiosaminide dimethyl acetal hydrochloride was subjected to drastic hydrolysis by alkali, methylamine was liberated. The methylamine was characterized by conversion to 2,4-dinitro-N-methylaniline. Since a methyl group might have migrated from oxygen to nitrogen under the influence of alkali,[6] it seemed advisable to carry out the alkaline hydrolysis after prior removal of the methoxyl groups from methyl streptobiosaminide dimethyl acetal hydrochloride by mild acid hydrolysis. This was done, and methylamine was again isolated and characterized. It may be concluded that the nitrogen atom in streptobiosamine is present as a methylamino group.

An examination of the reaction solutions of acid hydrolyses of streptomycin salts for the presence of low molecular weight cleavage products (*i.e.*, other than streptidine and streptobiosamine) did not yield positive results. A search for a volatile acid after alkaline hydrolysis revealed no acidic products other than those which could be accounted for by extensive decomposition of streptobiosamine.

The presence of a methyl group upon the nitrogen atom of streptobiosamine signifies a residual C_{12} structure, which is compatible with the disaccharide-like formulation. Since in all the known naturally occurring amino sugars the nitrogen atom is attached at position 2,[7] it seems likely that the methylamino group in streptobiosamine is at the 2-position of one hexose fragment.

These data and interpretations concerning the structure of streptomycin may be represented graphically as follows:



Acknowledgment. The authors wish to thank Dr. N. R. Trenner and Mrs. R. C. Anderson for the infrared and ultraviolet absorption measurements, Dr. J. B. Conn for the molecular weight determination, Mr. Richard N. Boos and his associates for microanalyses, and Mr. David Hendlin for assay data.

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QUINOID STRUCTURE AND BACTERIOSTATIC ACTIVITY

BACTERIOSTATIC activity of certain leucoderivatives of malachite green (tetramethyl-diamino-triphenyl-

[4] Kunz and Hudson, *Jour. Am. Chem. Soc.*, 48: 1982, 1926.

[5] Bryant and Smith, *Jour. Am. Chem. Soc.*, 57: 57, 1935.

[6] *Cf.* Irvine and Hynd, *Jour. Chem. Soc.*, 101: 1128, 1912.

[7] Gilman, "Organic Chemistry, An Advanced Treatise" (2nd Ed.), Vol. II, p. 1615. New York: John Wiley and Sons, Inc., 1943.

methane dye) has been related in a foregoing note.[1] The lability of these derivatives, however, makes it difficult to draw definitive conclusions concerning the relation between chemical structure and bacteriostatic activity.

We have now repeated these experiments with the diphenylmethane homologs of the above-mentioned derivatives. Although tetramethyl-diamino-diphenyl-methane dyes have a much weaker bacteriostatic activity than their triphenyl-methane homologs,[2] they offer, nevertheless, the advantage of forming more and stabler leucoderivatives, thus enabling the realization of more complete and more reliable comparative assays.

We have now found that the quinoid dye salts of tetramethyl-diamino-diphenylmethane (*i.e.*, dye salt of Michler's hydrol) and of tetramethyl-diamino-diphenyl (amino) methane (*i.e.*, auramine dye) are bacteriostatically active against *Staphylococcus aureus*, both of them practically at the same concentration (1:40,000).

The leucobases of both compounds, without quinoid structure, were inactive (to 1:5,000).

The methane-sulphonic derivative of Michler's hydrol, also a substance without quinoid structure, was equally inactive. This fact contrasts with our earlier observation according to which the triphenyl-methane homolog of the mentioned substance, *i.e.*, the bisulphite derivative of malachite green, showed a strong bacteriostatic activity in spite of its non-quinoid structure.[1] This bisulphite derivative is, however, an unstable substance ("vat dye"[3]), which transforms easily into the quinoid-structured dye salt, whereas its inactive diphenylmethane homolog has a stable non-quinoid character.[4]

Michler's ketone or tetramethyl-diamino-benzophenone, a non-quinoid substance, was inactive, and so was a series of other leucoderivatives of auramine and of Michler's hydrol (aminoethane nitril, aminoethanoilamide, hydroxyethanoilamide, aminoethanoic acid and hydroxyethanoic acid.[5]

Summary: Among various derivatives of tetramethyl-diamino-diphenylmethane only the quinoid-structured dye salts had bacteriostatic activity in our experiments, while the leucoderivatives were inactive.

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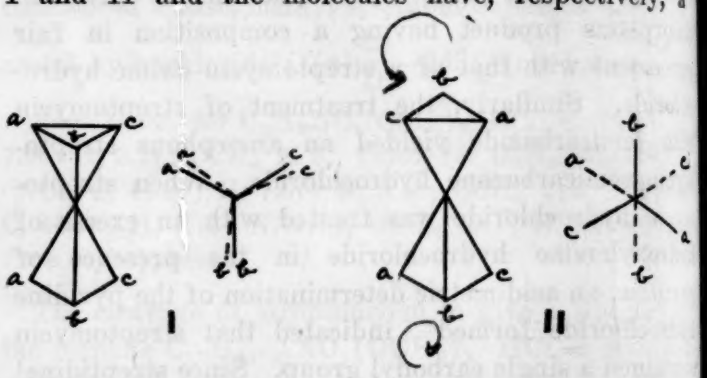
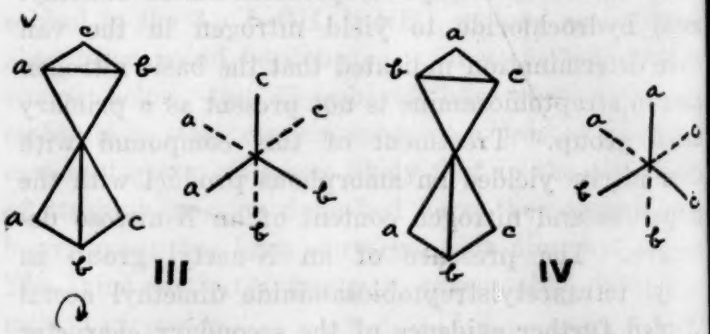
[1] E. Fischer, O. Hoffmann and E. Prado, SCIENCE, 100: 576, 1944.
[2] I. J. Kligler, *Jour. Exp. Med.*, 21: 463, 1918.
[3] H. Wieland, *Ber. deutsch. chem. Ges.*, 52: 880, 1919.
[4] H. Weil, *Ber. deutsch. chem. Ges.*, 27: 1403, 1894.
[5] K. Albrecht, *Ber. deutsch. chem. Ges.*, 27: 3294, 1894.

THE LACK OF MEANING OF THE PHRASE "INACTIVE BY INTERNAL COMPENSATION" AS APPLIED TO MESO COMPOUNDS

THE usual explanation of the inactivity of meso compounds given in both elementary and advanced texts is that the molecule consists of two asymmetric halves which are mirror images and hence rotate the plane of polarization equal amounts in opposite directions. The resulting compound is said to be "optically inactive by internal compensation." It frequently is recognized that the individual molecules would be inactive only when the groups occupy certain specified positions. For example, in the simplest case, the molecule Cabc Cabc is inactive only when the groups are in the positions corresponding to Figs. I and II and the molecules have, respectively, a



plane and a center of symmetry. In each case the mirror images are superimposable. In all other positions, however, for example, those illustrated by Figs. III and IV, there is no plane or center of sym-



metry, and the mirror image of the molecule is not superimposable. The explanation given for the non-existence of forms corresponding to III and IV is the same as that given for the non-existence of isomers of ethane and of 1,2-dichloroethane, namely, the assumption of "free rotation" about the single carbon-carbon bond. It is known, however, that in compounds such as 1,2-dichloroethane[1] and 1,2-dibromoethane,[2] rotation is not free, and that the mean

[1] Debye, *Physik. Z.*, 31: 142, 1930; Beach and Palmer, *Jour. Chem. Phys.*, 6: 639, 1938.
[2] Smyth and Kamerling, *Jour. Am. Chem. Soc.*, 53: 2988, 1931; Beach and Turkevitch, *ibid.*, 61: 303, 1939.

position of the atoms attached to the carbon atom is one in which they are staggered with respect to each other.

If II is the favored configuration, the molecule is inactive because it possesses a center of symmetry. Molecules corresponding to III and IV are active, and if IV is inverted, it becomes the mirror image of III; that is, they are enantiomorphs. Accordingly if III and IV should happen to be the most stable configurations, equal amounts of each would lead to a racemic mixture. One would not expect to be able to resolve it into the active components, however, because the barrier preventing free rotation usually would be low, and a molecule having configuration III and passing through configuration I would have an equal chance of returning to its original configuration or to that of its enantiomorph.

From chemical evidence in solution, it appears, in the case of meso 1,2-diaminosuccinic acid,[3] and meso dihydrobenzoin,[4] that the configuration corresponds to that of Fig. II, that is, the staggered position in which like groups are at the greatest possible distance from each other. On the other hand, the dipole moments of meso and racemic stilbene dichloride are 1.27 and 2.75, respectively, and those of meso and racemic dihydrobenzoin are 2.0 and 2.6. If free rotation existed, both meso and racemic forms should have identical moments. Moreover, if the meso stilbene dichloride molecule had a completely trans configuration analogous to Fig. II, the calculated moment is 0.52, while for free rotation it is 2.31.[5] Hence not only is rotation restricted somewhat but a considerable proportion of the molecules must have the unsymmetrical configurations of III and IV.

In the solid state the results of an x-ray investigation of meso erythritol are interpreted as indicating that this molecule has a center of symmetry.[6] However, in the case of anhydrous meso tartaric acid and of the dihydrate of its potassium salt, double molecules are present and the individual molecules are considered to be unsymmetrical.[7]

Therefore it may be concluded that the fact that the molecule has two similar asymmetric carbon atoms of opposite configuration has nothing whatever to do with the inactivity of meso compounds; that is, they are not inactive because of "internal compensation." They are inactive either because the molecules have a center of symmetry as in Fig. II, or because the enantiomorphs corresponding to Figs. III and IV are readily interconvertible, that is, readily racemized.

In the light of the above considerations, it immediately becomes obvious that if the groups on the ethane carbon atoms were large enough, rotation should be restricted sufficiently to permit the isolation of stable forms having configurations III and IV as well as configuration II. An examination of Stuart-type models indicates that such might be the case for α,β-dibromo-α,β-diiodosuccinic acid. Hence when the ethane carbon atoms of this compound have opposite configurations, it should exist in one resolvable racemic form and one meso form having a center of symmetry. In addition there should be three racemic modifications, instead of the usual one, when the ethane carbon atoms have like configurations. Moreover, tetraiodosuccinic acid should exist in a racemic as well as a meso modification. The possibility that these compounds would be chemically stable, however, is remote. Space relationships appear to prevent α,β-di-*ter*-butylsuccinic acid from existing in any configuration except that having a center of symmetry. There is a possibility that the chemical stability of α,α-dibromo-β,β-diiodosuccinic acid may be greater than that of α,β-dibromo-α,β-diiodosuccinic acid, and while the restriction of rotation appears to be less in the first compound, it may be sufficient to permit resolution.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A GLUTAMINE-RICH PEPTONE FOR CULTIVATION OF HEMOLYTIC STREPTOCOCCI

GLUTAMINE has been shown by McIlwain *et al.*[1] and by Bernheimer and Pappenheimer[2] to be a growth factor for various strains of hemolytic streptococci. Lankford and Snell[3] have found glutamine to be of importance also for the cultivation of fastidious strains of gonococci.

Since glutamine is costly and its preparation rather cumbersome, a convenient substitute for this material is desirable. Such a substitute has been found in a peptone prepared by tryptic digestion of gliadin, a protein rich in glutamine. The process is as follows: 2 g of pancreatin (Parke, Davis and Co.) is suspended in 30 cc of water, kept at 37° for 1½ hours,

[3] R. Kuhn and Zumstein, *Ber.*, 59: 479, 1926.
[4] Hermanns, *Z. physik. Chem.*, 113: 337, 1924.
[5] Weissberger and Saengewald, *Z. physik. Chem.*, B9: 133, 1930; B12: 399, 1931.
[6] Burgers, *Phil. Mag.*, [7] 1: 289, 1926.
[7] Schneider, *Z. Krist.*, 69: 49, 1928.

[1] H. McIlwain, P. Fildes, G. P. Gladstone and B. C. J. G. Knight, *Biochem. Jour.*, 33: 223, 1939.
[2] A. W. Bernheimer and A. M. Pappenheimer, Jr., *Jour. Bact.*, 43: 481, 1942.
[3] Ch. E. Lankford and E. E. Snell, *Jour. Bact.*, 45: 410, 1943.

and then centrifuged. The supernatant liquid is added to a suspension of 10 g gliadin (prepared from wheat gluten by extracting it with alcohol of 70 per cent.[4]) in 200 cc of water. The mixture is kept for one hour under toluene at 37°, then adjusted to pH 7–8 by addition of 0,1 N ammonia, and left over night at 37°. The next day the pH of the mixture is again brought to 7–8 by addition of ammonia. After being kept at 37° for an additional 4–5 hours, the mixture is heated for 15 minutes in a boiling water bath and is then filtered over night in the ice box. The filtrate is concentrated *in vacuo* to a volume of 50–70 cc. It is turbid at first, presumably due to presence of emulsified toluene, and becomes clear during the concentration. In order to avoid foaming during the concentration step, alcohol is constantly added dropwise from a dropping funnel whose tap has been opened to a suitable degree. To the concentrated solution absolute alcohol is added until a strong turbidity is produced. The turbid solution is then poured with stirring into ten volumes of absolute alcohol. The white flocculent precipitate is allowed to settle and is then filtered by suction, washed with absolute alcohol and dried in a vacuum desiccator over sulphuric acid. Yield, 4–4.5. The peptone is free of ammonium salts. On acid hydrolysis it yields 4.61–4.74 per cent. ammonia, which corresponds to a total glutamine content of about 40 per cent. if the small asparagine content of gliadin is neglected).

Gliadin peptone in a concentration of 20–40 mg per cent. effectively replaced glutamine as a growth factor for hemolytic streptococci in the medium of McIlwain *et al.* It has also been found that the gliadin peptone effectively replaces Bacto-peptone "Difco" employed by McIlwain *et al.* The following medium, which is entirely suitable for the growth of the streptococcus, has been adopted by us: glucose 0.5 per cent.; gliadin peptone 1.0 per cent.; NaCl 0.03 per cent.; Na_2HPO_4 12 H_2O 0.5 per cent.; KH_2PO_4 0.035 per cent.; $MgSO_4$ 7 H_2O 0.03 per cent. The substances should be dissolved in the order given, and the solution heated to boiling for ten minutes, filtered and then autoclaved at 15 pounds for 30 minutes. pH = 7.6. After cooling, the following sterile ingredients are added to the basal mixture: riboflavine, calcium pantothenate and thiamine in amounts of 100 micrograms per cent. The results of a typical experiment are shown in Table 1.

It has also been found by us[5] that α-methylamide and α-ethylamide of glutamic acid[6] fail to act as growth factors for hemolytic streptococci in the medium of McIlwain *et al.* McIlwain[7] has previously shown that N-acetylglutamine and a number of glutamine containing dipeptides (leucylglutamine, cysteylglutamine, glutaminylglycine, glutaminylcysteine and glutaminylglutamic acid) fail to replace glutamine as a growth factor for hemolytic streptococci. The results obtained with our peptone indicate therefore either that it contains free glutamine or that it contains peptides of glutamine which can be split hydrolytically by the proteases of the streptococci.

TABLE 1

GROWTH OF STREPTOCOCCUS HAEMOLYTICUS "RICHARDS." GROWTH AFTER 24 HOURS AT 37°

Medium		Photometer reading
McIlwain's medium without glutamine		97*
" " + glutamine	0.03 mg†	64
" " + "	0.1 "	58
" " + gliadin peptone‡	0.2 "	96.5
" " + " "	1.0 "	75
" " + " "	2.0 "	48
" " + " "	4.0 "	45
Gliadin peptone medium		54

* Growth was measured photometrically. The photometer reading of tubes containing water was adjusted to 100. Sterile medium then gave a reading of 97. Increasing growth is reflected by a decreasing reading.
† Amounts per 10 cc medium.
‡ The pure gliadin peptone solution was autoclaved at 15 pounds for 30 minutes.

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ESTIMATION OF CATHEPSIN ACTIVITY

RECENTLY Plentl and Page,[1] in a study of renin preparations, have stated that the hydrolysis of benzoylargininamide was not followed quantitatively by an increase in titratable carboxyl groups since, with the concentrations of protein required, the large amount of precipitate formed during the titration masked the color change of the indicator. The procedure referred to[2] is that of Grassmann and Heyde.[3] Since this method has become so important in the kinetics of proteinase action,[4] and in order that others might not be discouraged, it seems worth while to point out that the above-mentioned difficulty was encountered in a similar case and circumvented not long ago.[5]

[4] Th. B. Osborne and E. Strauss, Abderhalden's "Handbuch der biologischen Arbeitsmethoden," I: 8, 437, 1922.
[5] With collaboration of Mrs. J. Storch-Levy.
[6] N. Lichtenstein, *Jour. Am. Chem. Soc.*, 64: 1021, 1942.
[7] H. McIlwain, *Biochem. Jour.*, 33: 1942, 1933.
[1] A. A. Plentl and I. H. Page, *Jour. Biol. Chem.*, 155: 368, 1944.
[2] K. Hofmann and N. Bergmann, *Jour. Biol. Chem.*, 130: 81, 1939.
[3] W. Grassmann and W. Heyde, *Zeits. Physiol. Chem.*, 183: 32, 1929.
[4] G. W. Irving, J. S. Fruton and Max Bergmann, *Jour. Biol. Chem.*, 138: 231, 1941.
[5] F. M. Uber and A. D. McLaren, *Jour. Biol. Chem.*, 141: 234, 1941.

The Grassmann and Heyde method calls for the titration of *alpha*-aminocarboxylic substances with alcoholic KOH to an endpoint with thymolphthalein comparable in depth of color to that of a dilute, ammoniacal $CuCl_2$ solution. If to the color standard there is added a small amount of freshly precipitated $BaSO_4$, a turbidity is produced similar to that resulting from the precipitation of enzyme in the titration mixture. With this procedure, and a white box illuminated by a "daylight" bulb, data suitable for the calculation of reaction constants for trypsin were acquired.[5]

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DISCUSSION

BIOLOGY IN THE PREMEDICAL CURRICULUM

MANY colleges and universities are in the process of reevaluating their aims and teaching methods and of revising their curricula. The preprofessional curricula are necessarily affected by these changes. As far as the premedical curriculum is concerned, it is fortunate that medical schools and colleges seem to be in agreement on the basic principles on which this program should be based. Spokesmen of the American Association of Medical Colleges[1,2] as well as individual administrators and teachers of medical schools have repeatedly stressed the necessity of a broad cultural background rather than a narrow and specialized training in sciences, as the basis for the medical school and medical profession. For the medical student, an appreciation of arts and literature and an insight into social institutions and their history is deemed just as necessary as a thorough grounding in the natural sciences. The foundation for these qualifications must be laid in the college, which means that in a premedical curriculum the humanities, social sciences and natural sciences should be well balanced. Since the liberal colleges stand for the same general principle, there should be no difficulty in fitting the premedical program into the framework of an A.B. curriculum, by making allowance for the special needs of premedical students and by giving flexibility to the program of those who do not intend to take the A.B. degree. The difficulties become apparent when details are considered. Many difficulties arise from the fact that the entrance requirements of different medical schools differ widely. A more serious dilemma faces the sciences. If the principle outlined above is to be adopted sincerely, then premedical students should not be encouraged to specialize in natural sciences except in the case of those students who are especially gifted for them. On the other hand, those aspects of physics, chemistry and biology which are of importance for medicine grow steadily; so much so that, for instance, soon the need for a second year of physics may become urgent. The situation is aggravated by the prospect that in the future many, if not the majority of all premedical students will not stay for more than three years in college. This means that the natural sciences are forced to accomplish more in a shorter time. It is urgently necessary that we scrutinize carefully and rigorously the contents of the courses which we offer to premedical students, and that we improve the efficiency of our teaching methods.

Last summer a small group of biologists and two members of medical schools met at the Marine Biological Laboratory in Woods Hole for an informal discussion of some of these problems as far as they concern the role of biology in the premedical curriculum. Those present were Ph. Armstrong, Syracuse University Medical School; E. Ball, Harvard University Medical School; L. V. Heilbrunn, Department of Zoology, University of Pennsylvania; R. Kempton, Department of Zoology, Vassar College; D. Marsland, Department of Biology, New York University; A. K. Parpart, Department of Biology, Princeton University; A. W. Pollister, Department of Zoology, Columbia University; W. R. Taylor, Department of Botany, University of Michigan, and the writer. It was felt by the group that some of the conclusions reached in this conference might be of a more general interest and might serve as a basis for further discussion. It should be stated that the participants expressed their personal opinions and not those of any organizations or institutions. Furthermore, this report is based on the spontaneous discussion which developed during the conference and makes no claim to cover the ground adequately. The following ten points present the edited and somewhat enlarged protocol of the meeting.

(1) The entrance requirements of the different medical schools differ widely from each other (see the tabulation of Swett[3]). The premedical curricula of colleges are even more diversified, due to local conditions and traditions, and because the colleges have the responsibility of preparing premedical students for more than one medical school. We recognized fully that a certain degree of diversity is desirable and also inevitable, but it was felt that at present there exists too much variation. As a result the stu-

[1] W. C. Rappleye, *Jour. Assoc. Am. Med. Coll.*, 15: 221–227, 1940.

[2] F. C. Zapffe, *ibid.*, 15: 228–234, 1940.

[3] F. H. Swett, *ibid.*, 15: 385–386, 1940.

dents entering medical schools differ widely in the degree of preparation, which may be a handicap for instructors in medical schools. Representatives of the medical schools should get together with representatives of the biological societies to work out a more uniform framework of prerequisites which could still leave room for sufficient diversity. As long as the present conditions exist the Association of American Medical Colleges would render a real service to biologists and college administrators if it would publish in its journal, at frequent intervals, a tabulation of the entrance requirements of all medical schools, similar to the tabulation of Swett.[3]

Concerning the Elementary Courses in Biology

(2) There was general agreement that elementary courses for premedical students should under all circumstances include laboratory work.

(3) Since a number of colleges have adopted, or will adopt, a terminal introductory course in biology in which the laboratory work will be reduced and, in part, replaced by demonstrations, films, etc., the question arises whether a separate parallel course, including laboratory work, should be offered to premedical students. We agreed that there can be no universal answer to this question; in many institutions the staff may be too small to make such a split feasible. However, the question deserves serious consideration. It may be argued on the one hand that a general introductory college course should present the basic concepts of biology in such a manner that the course would be as profitable for preprofessional students as for non-science students. On the other hand premedical students are a selected group, many of whom have a special interest in natural sciences and are better prepared for them. It should be possible to give those students a more comprehensive course at a more rapid pace. Many of us have had satisfactory experiences along that line with the selected groups of Army and Navy students. Since the majority of the premedical students will probably have to be prepared in three years, a rigorous training from the start would be advisable.

(4) The role of botany in a general biology course has been much debated. To what extent should botany be included? Should botany and zoology be taught in separate courses or as an integrated unit? We agreed that either arrangement may yield satisfactory results and that the local situation in the different institutions should decide which procedure is to be followed.

(5) It was agreed that it would be advantageous if a course in chemistry would precede the introductory biology course. Those who have had experience with this arrangement reported very satisfactory results.

Concerning Anatomy and Embryology

(6) The question was raised whether embryology should be required of all premedical students. The answer was in the affirmative. A knowledge of the elements of embryology is necessary for the medical students. Those who have had no embryology either in college or in the medical school are at a disadvantage. Some medical schools are aware of this need and offer embryology courses, but such courses are likely to emphasize human or mammalian embryology only. College courses in which the general principles are stressed would be more desirable.

(7) It was felt that the elements of vertebrate anatomy are likewise an essential part of the premedical curriculum. They may be offered in a special course or be included in a comprehensive elementary course. We all agreed that a course in cat anatomy is not essential or advisable. It defeats one of the main purposes of the anatomy course: to give the student a broad comparative and historical point of view of vertebrate organization, before he begins to limit his study to one single form, the human.

Concerning Advanced Courses

(8) The group was of the opinion that a course in general physiology would be very helpful, since the average student entering medical school is unaccustomed to the ways of physiological thinking. However, such a course should not be a dilute mammalian physiology course but give an understanding of basic phenomena, such as cell respiration, nutrition, irritability. The study of the physiology of vertebrate organs is coming more and more to be dependent on cell physiology. For properly taught courses in general physiology, the student is urged to apply his knowledge of chemistry and physics to physiological techniques and physiological interpretation. This is highly advantageous, and the premedical student, accordingly, should defer his course in general physiology until he has completed his courses in physics and chemistry.

(9) Just as mammalian physiology would be an unnecessary and undesirable duplication of a medical school course so would be other courses of medical content, such as histology, bacteriology or medical parasitology.

(10) Genetics should be more strongly emphasized in the premedical curriculum. The ignorance of most medical students in matters of genetics is pitiful. Yet the importance of genetics for many problems in medicine and public health becomes so obvious that a few medical schools have already organized courses in medical genetics. Again, college courses stressing the fundamentals rather than the application to medicine would be preferable. The traditional Drosophila laboratory-course may be too specialized in the other

direction. A new type of genetics course might be developed in which elementary principles, physiological genetics and the application of genetics to the human being would be emphasized.

Another important point was briefly mentioned but not discussed at the Woods Hole meeting: The frequent complaint of medical school instructors that the college fails most seriously in the formal education of the students. Their faculty of logical reasoning and of independent thinking are not sufficiently developed. They are not able to draw simple conclusions from premises. They have not acquired the ability to express themselves concisely in words or in writing. I believe that these criticisms are by and large justified. The fault lies in part with our teaching methods. We are apt to apply without discrimination the methods of elementary courses to the junior and senior level, where they do not belong. A number of colleges and universities have gone a long way towards improving this situation, but much remains to be done. It is suggested that a new seminar or discussion type of an advanced course be designed in which the formal lectures are reduced to a minimum. Instead, the students would be guided to discuss and evaluate phenomena observed in the laboratory or demonstrated by slides; to formulate conclusions and explanations; to suggest further experiments, and to present short reports. In this way, an atmosphere can be built up in which the emphasis is not on memorized facts, lecture notes, examinations and grades, but on the satisfaction derived from independent thinking and the insight into the scientific method. The subject matter of such a course would be of secondary importance. We have had excellent results along these lines in a summer course organized in conjunction with Washington University Medical School, in which problems of growth, experimental embryology and developmental genetics served as the basis for the discussions.

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SUPPRESSION OF VITAL DATA

THE publication of the results of research is intended to inform the world, and above all the scientists engaged in parallel investigations, of the progress made; that prestige attaches to priority in publication is relatively a trivial consideration. A claim for priority should be explicit enough to show belated rivals whether their work is still sufficiently different in method from that of the first-comers to be worth completing. The scientist is not bound to broadcast his hopes for the future of the research, nor to commit himself in print to beliefs not fully secured by experiment; on the other hand, he is, surely, not entitled to suppress uncontroversial facts that are essential to understanding and appraisal of his paper. Thus Hutchings and others[1] must have known, but did not mention, the source from which they isolated a new *Lactobacillus casei* factor; and though synthesis is not always an unequivocal proof of chemical constitution, SubbaRow and others[2] must have known, but did not mention, at least the starting point and procedures selected for their synthesis of a compound apparently identical with the *L. casei* factor from liver. It is not to be supposed that it was considerations of national security that dictated this omission of vital information. The columns of SCIENCE should not be open to communications of this kind.

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THE YALE CYCADEOIDS

ONE hundred years ago the famous Buckland finely illustrated the Dinosaurs and other ancient reptiles of South England. Also well illustrated, were low and bulky accompanying petrified plants correctly inferred to have some relation to "sago palms." These, however, were not well understood and remained relatively unstudied, as had isolated types from the Carpathians and elsewhere in Europe.

The final and inescapable incentive to acute structural study of the sago-palm relatives or "fossil cycads" was yet to come from the vast assemblage of specimens which came into view in the Mesozoic Rim of the Black Hills of South Dakota and Wyoming from 1893 on. It was presently found that counting the more isolated finds the Hills were girdled by occurrences of the fossil cycads, with some vertical distribution in the latest Jurassic and lowermost Cretaceous. The Dinosaurians were also found present in vast array.

Such an array could not escape that acutely aggressive assembler of paleontologic evidence, O. C. Marsh, of Yale. He at once made extensive purchases from local fossil hunters about the Hills. And then, when the dinosaur *Barosaurus* was collected at Piedmont by Wieland as Marsh's student, the "cycads" took on an immense meaning. The acute study was begun. The collections were signally added to, so that now the Yale collection of fossil cycads perhaps equals all other such collections put together. Their study, as extended to the more severely scientific viewpoints, has led to the publication of splendidly illustrated quarto volumes as brought out with the aid of the Carnegie Institution of Washington. Also, collateral

[1] B. L. Hutchings and others, SCIENCE, 99: 371, 1944.
[2] Y. SubbaRow and others, SCIENCE, 102: 227, 1945.

study has been extended to Mexico and Patagonia, with moreover most careful elaboration of the likewise finely silicified but rare types of the Carpathians.

The preliminary approach to the Yale cycad study was perforce macroscopic, as arranged by Marsh with Lester F. Ward. That meant an arbitrary naming of species. But that was no less the severely practical line of approach. As Ward well said, the cycadeoid series was to the plant life of the Mesozoic what the dinosaurs were in that animal world.

The closer study of the cycads, with the initial help and advice of Marsh and Ward, was nextly carried forward by Wieland, attention being given to both structure and further collection in the field. By 1906, the first quarto on the American Fossil Cycads was brought out. Then, that fine paleobotanist of all time, D. H. Scott, said, "The brilliant elucidation of the American Fossil Cycads by Dr. Wieland at Yale has for the first time brought the origin of the modern types of flowering plants within the range of scientific discussion." A new chapter had been added to the paleontologic texts.

Moreover, the work has gone on in the laboratory and the field, but with many difficult and varied tasks yet ahead. Change within Yale has resulted in removal and restorage of the tons of material, following the dismantling of the old Peabody Museum, four times. The great collections are safe, but far from clearly in view for either purposes of study or exhibition. The related studies of Mesozoic floras indicated as severely needed have about lapsed.

In for the present closing these brief notations, two pleasant interludes must be recorded. By accident in 1927 following a detour in the Black Hills it was learned that a large once flowering type had been found in the "Mesaverde" series of the San Juan basin of New Mexico. This was the sixth such type from the known world. Aggressive examination of the new field of occurrence followed in the summers of 1928 and 1929. This surpassed expectation. Two tons of the new types were secured and have been freely cut and preliminarily described under the new generic name *Monanthesia* or once flowering. Several distinct species are present, and the descriptive memoir with free illustration is now well forward. An addition to Yale collections and to the great subject of cycadeoid study of a fascinating interest is here seen. There followed the November, 1935, collection of one ton of *in situ* specimens on the front mesa of the Fossil Cycad National Monument. Work afield is never safely to be neglected, is ever fully as important as laboratory study.

The 1935 Fossil Cycad National Monument collection is now stored at Yale for safe keeping, against the day of return for exhibit in the museum yet to be erected on the frontal mesa of the Monument.

The plans for bringing to the fore the immense educational value of the F C N M have been freely discussed in print, and are slowly reaching clear understanding. In few words, the Monument is a contribution from the Carnegie Institution and Yale dedicated to the cause of science through the centuries to come. The Bureau of National Parks and Monuments has in course come into a great responsibility. For the Monument marks the finest cycadeoid locality yet found on the globe and must be held sacred, intact and free from theft or trespass as an educational point of both international interest and surpassing value. The closest analogue yet remains hidden in the Galician Carpathians.

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SCIENTIFIC BOOKS

GENETICS

Genetics. By EDGAR ALTENBURG. xii + 452 pp. Illustrated. New York: Henry Holt and Company. 1945. $3.20.

THE publication of a new text-book in genetics is a rather rare event. Several good texts are available, and the market in terms of number of students is limited if compared with that of books on general biology, college physics or similar introductory topics. The purpose of a college course in genetics is less well defined than that of many other courses. Some of the advances in genetics have so far outrun possible practical applications that they are of less immediate preprofessional use than, for instance, the facts of chordate anatomy to the student planning to enter a medical school, or physical chemistry to the future chemist. Nor is a course in genetics a generally recognized prerequisite for advanced work in fields other than genetics itself. Primarily then, a course in genetics is offered because this science has become a basic branch of biology, one about which the student should be informed.

Altenburg's book serves this purpose admirably. The author states in his preface that in preparing the manuscript he constantly asked himself, "Could I understand this if I were the student?" The text bears witness to this self-questioning of an experienced teacher. While a great many aspects of genetics are covered within 452 pages, the treatment is never too condensed, and singles out skilfully for detailed discussion many points of special importance or of potential difficulty. Consequently, the

book serves not only as an elementary introduction but leads successfully to a lucid treatment of many advanced and complex groups of investigations such as "Locating the breakage points in a translocation," construction of cytogenetic maps or the cases of complex heterozygotes (Oenothera).

An unusual feature of the book is the presence of itemized summaries of from one to three pages at the end of each chapter. These should prove very useful to the student. Numerous problems furnish an opportunity for applying knowledge gained from the text and also include additional information.

The book is not only centered around the chromosomal aspects of genetics but is devoted to it nearly exclusively. This results in an insufficient discussion of physiologic and of population genetics. Little space is given to human inheritance or to extranuclear transmissions. The treatment of Mendel's principles and of most other topics follows in general the scheme: (1) statement of theorem; (2) experimental proof. This enables the student to recognize the essential point immediately, but the reverse sequence, namely, (1) experiment; (2) deduction of theory, would have its merit too. While the information supplied is identical in both sequences, the latter seems better suited to convey the exciting pleasure of the discovery and organically makes possible a historical treatment with its humanistic implications. Altenburg does not neglect historical references but provides them as afterthoughts. Besides, the selection and omission of names of investigators is not free from subjectivity.

It is difficult to avoid errors in a first edition of a book which seems not to have been read critically in manuscript by colleagues of the author. A list of such errors has been placed at the author's disposal for use in later editions. For in spite of the criticisms voiced, this is an excellent book. There seems no doubt that Altenburg's "Genetics" will occupy a prominent place in the teaching of this subject.

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PLANTS AND CULTURE HISTORY

Plant Geography and Culture History in the American Southwest. By GEORGE F. CARTER. 140 pp. New York: Viking Fund Publications in Anthropology. 1945. $1.50.

IN this volume Carter has assembled a variety of data, archeological, ethnological, historical, geographical and taxonomic on the economic plants of the Southwestern cultures, has combined these with the results of his own research, and has drawn some far-reaching conclusions from the combination.

On the basis of the distribution, past and present, of cultivated plants Carter divides the agriculture of the Southwest into two areas—the Gila-Sonora and the Anasazi.

The Gila-Sonora area includes approximately the southern halves of Arizona and New Mexico, is associated with the Piman and Yuman cultures, is characterized botanically by the summer squash, *Cucurbita Pepo,* a single race of maize, tepary and lima beans, and cotton. Carter traces its origins directly to Mexico and regards it as relatively recent.

The Anasazi area represents the plateau agriculture which is associated with the Basket Maker and Pueblo cultures. It is characterized botanically by the cushaw type of pumpkin, *C. moschata,* the kidney bean and several types of maize, some of which show strong resemblances to those of the eastern United States. Carter regards the earliest culture of this area, the Basket Maker, as a peripheral development springing from an earlier eastern agriculture which had originated independently of Mexico and was based upon the growing of locally domesticated cucurbits and the utilization of seeds of Chenopodium, Ambrosia and Helianthus.

Carter's conclusions with regard to the Southwest have important implications for other regions. The first is obvious—if the earliest cultures in the Southwest have had their origins in eastern precursors then it follows that the latter must be considerably earlier than has commonly been supposed, perhaps, by Carter's reasoning, as early as Upper Pleistocene. A second implication is that domesticated plants (and by inference other cultural materials) have reached the region now the United States by two routes, one west Mexican, the other east Mexican or Caribbean. The third implication is that domestication of plants and the invention of agriculture have occurred in America independently again and again, indeed wherever plants suitable for domestication were available. Carter postulates four centers of domestication for *Cucurbita Pepo* alone.

To a botanist who holds the deep conviction that botanical studies of prehistoric plant material need not end with mere description, a first, cursory reading of Carter's book brings only delight. But further study raises serious doubts. Is the evidence adequate to support the important conclusions drawn from it? The evidence from maize, at least, is far from satisfactory. It deals with plant differences at a varietal or racial level. Progress has been made in recent years in identifying and describing the races of maize, but the problem is so complex, and intermixture between races is so wide-spread, that the conclusions which Carter has drawn from his studies of maize involve an appreciable element of doubt as well as one

serious error. Carter states that the earliest Basket Maker corn is uniformly flint in kernel texture, yet of the 33 ears found at the earliest-dated Basket Maker site, only 18 were classified by G. N. Collins, a maize expert, as flint. The evidence from the cucurbits is, in the final analysis, scarcely mere convincing—it is easily susceptible of more than one interpretation. The treatise suffers also from a failure to distinguish always between conjecture and fact—there is a tendency for the tentative hypothesis of one page to be treated as an established fact on another.

The archeologist is inclined to criticize even more severely. To him it seems that Carter has not only treated the published literature in archeology in a highly selective manner to create an impressive and forceful "one-way" argument in support of his hypotheses, but that he has also made some rather conspicuous errors. The assumption that "Basket Maker agricultural beginnings must lie either to the South, *i.e.*, among the Hohokam, or derive from some eastern source . . ." seems unwarranted on the basis of the known evidence. There is a great deal more than the Hohokam to the south of the Anasazi country as Carter defines it. Indeed the Hohokam cultures are largely restricted to the Gila Basin in Arizona and have only a limited spread.

Carter's discussion of geographical factors will seem peculiar to archeologists. In presenting his argument that agricultural plants and practices diffused into the Pueblo area from the Mississippi Valley he seems to ignore the known trade routes of Coahuila and the valleys of the Rio Grande, Pecos, Colorado of Texas and the Brazos; all covered in archeological discussions of prehistoric shell trade. In this same connection it seems unwise to ignore the cave material from Coahuila, the Upper Gila and Upper Salt, and other southern areas, which many students consider to be related, at least, to Basket Maker. On this point the archeologists must bear a share of the blame for slowness in publication.

The theory of the route through the Mississippi valley seems to be weakened also by the negative evidence of the Ozark caves. Carter presents the Ozark Bluff Dweller culture as representing the earliest agricultural stage in the eastern United States. Then he states that Basket Maker agriculture could not have derived from that.

In brief, his conclusions run counter to all archeological theory and evidence, and must therefore stand entirely on the botanical evidence.

Carter makes a strong point of the presence of ditch irrigation in the Hohokam area and its absence in the Pueblo region to the north. Here he is merely following careless statements in the general archeological literature of the Southwest. Ditch irrigation was practised in the Pueblo area and as far north as the Mesa Verde region of the San Juan in southwestern Colorado and southeastern Utah. Reservoirs and ditches were first noted in that country by Nordenskiold in 1893, and have since been described by others.[1]

The last section of the book is devoted to an argument for a great age of human cultures based upon the evidence from plant domestication. Here Carter makes use of a technique which he apparently denies to archeologists. In criticizing Gladwin's early dating of the Snaketown culture he says, "Gladwin's early dates are based on the theoretical time necessary for cultural developments which took place. This is obviously a risky means of arriving at a date." Archeologists will think that it is also a risky means of arriving at botanical dates.

Despite the criticisms which can be made of it the book still remains an important contribution and one which both botanists and archeologists will read with interest.

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[1] *Cf.* Guy R. Stewart and Maurice Donnelly, *Scientific Monthly*, 56: 1 and 2, pp. 31–44, 134–144, 1943.

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